ARTICLE

Prognostic Utility of Magnetic Resonance Imaging in Neonatal Hypoxic-Ischemic Encephalopathy

Substudy of a Randomized Trial

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Objective: To investigate the effects of hypothermia treatment on magnetic resonance imaging (MRI) patterns of brain injury in newborns with hypoxic-ischemic encephalopathy compared with normothermia, including the prognostic utility of MRI for death and/or disability at a postnatal age of 2 years.

Design: Substudy of a randomized controlled trial.

Setting: Participating centers in the Infant Cooling Evaluation trial.

Participants: Trial participants (gestational age ≥35 weeks with moderate to severe hypoxic-ischemic encephalopathy, randomized to whole-body hypothermia or normothermia) with available MRIs.

Main Exposure: We performed qualitative evaluation of T1- and T2-weighted and diffusion MRIs. The posterior limb of the internal capsule was classified as normal or abnormal, whereas the basal ganglia and thalami, white matter, and cortical gray matter were classified as normal or mildly abnormal or moderately/severely abnormal.

Main Outcome Measures: Death or major disability at 2 years.

Results: We evaluated 127 MRIs (66 patients treated with hypothermia and 61 with normothermia; mean age at scan, 6 postnatal days). The odds of having moderate/severe white matter or cortical gray matter abnormalities on T1- and T2-weighted MRI were reduced by hypothermia (white matter odds ratio, 0.28 [95% CI, 0.09-0.82]; gray matter odds ratio, 0.41 [0.17-1.00]). Abnormal MRI findings predicted adverse outcomes, with T1- and T2-weighted and diffusion MRI abnormalities in the posterior limb of the internal capsule and basal ganglia and thalami demonstrating the greatest predictive value. There was little evidence that prognostic value of the MRI was modified by therapeutic hypothermia (all interactions, $P > .05$).

Conclusions: Brain injury on T1- and T2-weighted MRI is reduced in hypothermia-treated newborns. Abnormal MRI findings are prognostic of long-term outcome in moderate to severe hypoxic-ischemic encephalopathy regardless of treatment with hypothermia.

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HYPOXIC-ISCHEMIC ENcephalopathy (HIE) in term and near-term newborns is an important cause of morbidity and mortality.[1,2] Therapeutic hypothermia has been a major advance in the management of neonatal HIE. Meta-analyses of several large multicenter trials have concluded that

For editorial comment see page 669

hypothermia treatment is associated with a reduction in death and neurological impairment in early childhood.[3-9] These results were confirmed in the recently reported Infant Cooling Evaluation (ICE) randomized controlled trial, in which whole-body hypothermia treatment was shown to reduce death or major sensorineural disability at 2 years of age compared with normothermia.[7]

Magnetic resonance imaging (MRI) assists in defining the nature and extent of perinatal brain injury. Because hypoxic-ischemic (HI) cerebral injury is a dynamic process, the diagnostic and prognostic utility of MRI needs to be interpreted in the context of the timing of the MRI. Patterns of brain injury on conventional T1- and T2-weighted MRI at 1 week after birth have been shown to predict abnormal neuromotor outcome in early childhood.[10] Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) changes with HI injury are most prominent from days 2 through 5 and can be detected earlier than abnormalities detected on the conventional T1- and T2-weighted MRI.[11] In the Total Body Hypothermia for Neonatal Encephalopathy

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(TOBY) trial, MRI studies performed a median of 8 days after birth reported a reduction in the incidence of cerebral injury compared with normothermia but consistent prognostic value from MRI irrespective of treatment.[12] However, we need to determine whether this prognostic utility is similar in a different cohort with MRI performed at a different median age.

The aims of this study were to investigate (1) the effects of hypothermia on MRI patterns of brain injury compared with normothermia; (2) the prognostic utility of MRI in moderate to severe HIE for predicting death or major disability at 2 years; and (3) whether this prognostic utility is affected by hypothermia treatment. We hypothesized that the proportion of newborns with significant cerebral lesions characteristic of HIE on MRI would be reduced in those treated with hypothermia, that MRI would be prognostic of death or major disability at 2 years of age, and that the prognostic utility of MRI would not be altered by hypothermia treatment.

METHODS

PATIENTS

This study is a substudy of the ICE trial, a multicenter, international, randomized controlled trial of moderate whole-body hypothermia compared with standard care in newborns of at least 35 weeks' gestation with moderate or severe clinical encephalopathy and evidence of peripartum HI (defined as 2 of the following criteria: Apgar score ≤5 at 10 minutes, continued need for mechanical ventilation at 10 minutes, and metabolic acidosis [cord or an arterial, venous, or capillary pH of <7.00 or base deficit ≥12 mEq/L within 60 minutes of birth]).[7] Newborns in the ICE trial were recruited at birth from 28 centers across Australia, New Zealand, Canada, and the United States from February 14, 2001, through July 27, 2007, and were randomized to whole-body hypothermia (target temperature, 33.5°C; range, 33°C-34°C) or normothermia (target temperature, 37°C; range, 36.8°C-37.3°C) within the first 6 hours after birth and continuing for 72 hours. This substudy includes ICE participants who had MRIs made available for independent assessment. The trial protocol was approved by the Human Research and Ethics committees of each of the 28 participating sites.

MRI METHODS

Participants in the ICE study underwent MRI within the first 10 days after birth with conventional T1- and T2-weighted MRI, DWI, and ADC sequences at 1.5 T or 3.0 T according to the participating site's clinical practice. Images made available for this substudy were assessed by 3 investigators experienced in neonatal neuroimaging who were not part of the ICE trial (J.L.Y.C., L.C., and R.W.H.) and who were blinded to treatment allocation and the clinical details of the participants, apart from gestational age at birth and postnatal age at the time of MRI. Images considered to be inadequate for analysis were excluded. Images were evaluated by each investigator and results compared; any disagreement was resolved by consensus. The pattern of brain injury was classified according to abnormalities in brain regions known to be susceptible in HIE, based on Rutherford et al.[12] For conventional T1- and T2-weighted MRIs and DWIs, the following regions were systematically classified.

1. The posterior limb of the internal capsule (PLIC) was classified as normal or abnormal, in which abnormality was determined by a reduced or absent signal intensity on T1- or T2-weighted sequences and/or by qualitatively assessed, abnormally restricted or increased diffusion on DWI. Areas of restricted diffusion on DWI were confirmed by areas of reduced signal on the ADC map.
2. The basal ganglia and thalamus (BGT) were classified as normal/mild abnormality if no or minimal focal signal abnormality on T1- or T2-weighted sequences and/or normal diffusion characteristics were noted and as moderate/severe abnormality if multifocal or widespread abnormalities were noted on T1- or T2-weighted signal and/or by qualitative abnormality on DWI and ADC sequences.
3. The white matter was classified as normal/mild abnormality if no or mild signal abnormality on T1- or T2-weighted sequences and/or normal diffusion characteristics were noted. Moderate/severe white matter abnormality was assigned if signal abnormalities or qualitative diffusion abnormalities (restricted ADC) extended to the subcortical white matter or if more than 3 regions of abnormal white matter were found.
4. The cortical gray matter was classified as normal/mild abnormality if no or mild signal abnormality on T1- or T2-weighted sequences or qualitative diffusion abnormalities in 2 or fewer sites (including the central sulcus, interhemispheric fissure, and insula region) were noted. Moderate/severe cortical gray matter abnormality referred to more extensive involvement.

Examples of the MRI classification are demonstrated in **Figures 1**, **2**, and **3**.

NEURODEVELOPMENTAL OUTCOME

The primary composite outcome of the ICE trial was death or major sensorineural disability at 2 years of postnatal age. *Major sensorineural disability* was defined as having neuromotor delay, developmental delay, blindness (vision worse than 20/200 OU), and/or deafness requiring amplification or worse. *Neuromotor delay* was defined as cerebral palsy in which the child was not walking at 2 years of age, Psychomotor Development scores on the Bayley Scales of Infant Development (BSID) II or Motor Composite Scale score on the BSID III were 2 SDs or less, or disability level on the Gross Motor Function Classification System ranged from II to V.[13,14] *Developmental delay* consisted of a Mental Development Index score on the BSID II or Cognitive or Language Composite Scale scores on the BSID III of 2 SDs or less.[13,15,16]

STATISTICAL ANALYSIS

Data were analyzed using commercially available statistical software (STATA, version 11.0; StataCorp). The MRI characteristics were compared between the treatment groups using separate logistic regression models for each of the T1- and T2-weighted and diffusion variables, with results presented as odds ratios (ORs) with 95% CIs. The MRI variables were investigated as predictors of death or major sensorineural disability at 2 years of age using logistic regression adjusted for treatment group. Initially, each MRI variable was assessed as a predictor of outcome in a separate regression model. In these univariable models, whether the relationship between the MRI variable and outcome was the same in the hypothermia and standard care groups was assessed by allowing for a different effect of the MRI variables in the 2 treatment groups (an interaction effect). In view of the potential influence of the day of MRI on prognostic utility, we repeated the analysis including age at MRI as a covariate. Next, we analyzed MRI variables in a combined model (one for conventional T1- and T2-weighted abnormalities and another for diffusion abnormalities) to determine in-

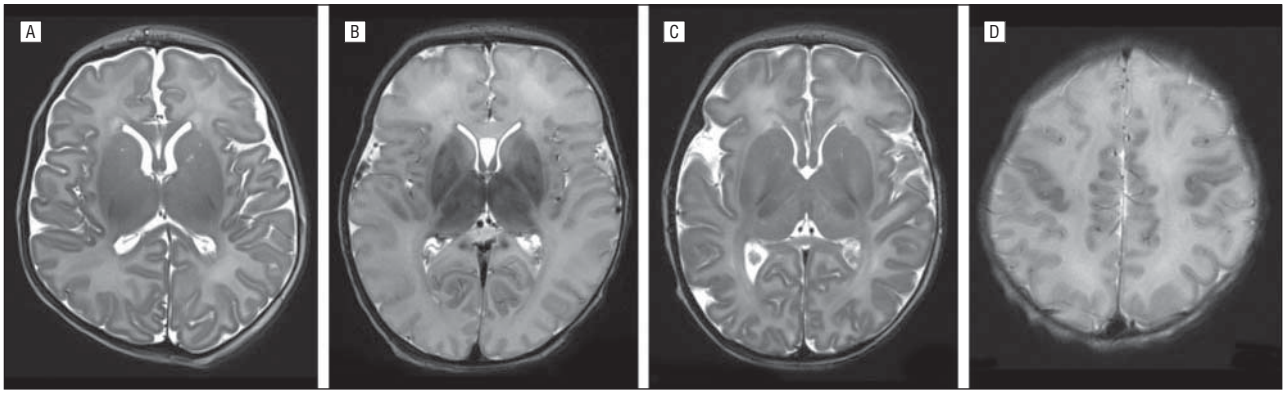

Figure 1. Appearance of hypoxic-ischemic encephalopathy on T2-weighted axial magnetic resonance imaging. A, A normal brain in a term newborn with myelination in the posterior limb of the internal capsule (PLIC). B, Severely abnormal basal ganglia and thalamus (BGT) lesions, absent myelination of the PLIC, and abnormal signal in the white matter, especially in the frontal lobes. C, Moderately abnormal BGT involving the putamen and thalamus, with myelination of the PLIC present. D, Abnormal signal in the Rolandic cortex.

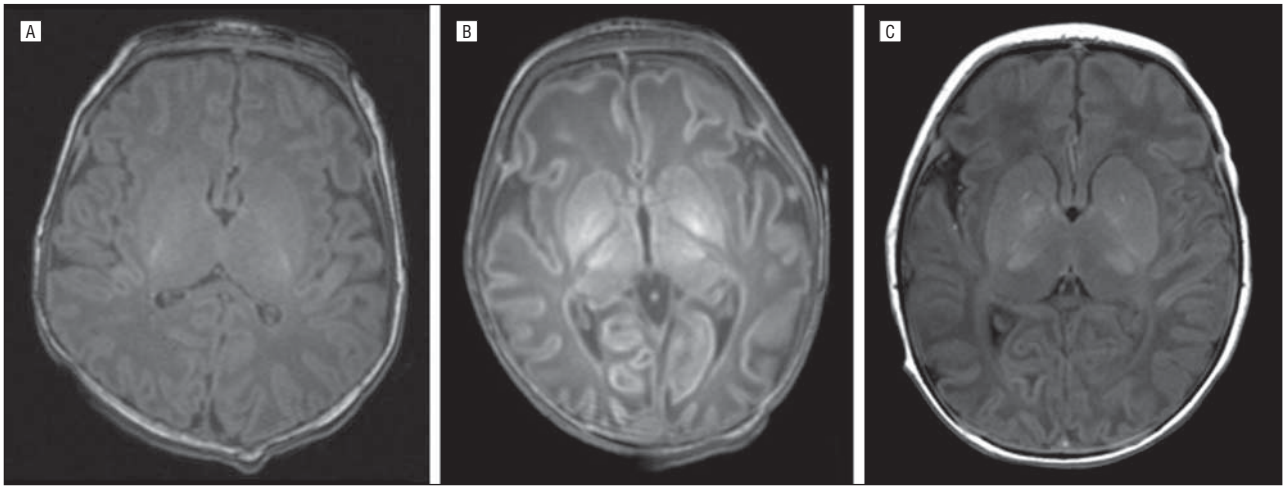

Figure 2. Appearance of hypoxic-ischemic encephalopathy on T1-weighted axial magnetic resonance imaging. A, A normal brain in a term newborn. B, Severely abnormal basal ganglia and thalami (BGT), absent myelination in the posterior limb of the internal capsule (PLIC), and widespread abnormal cortical gray matter. C, Moderately abnormal BGT signal involving the putamen and thalamus, with myelination of the PLIC present.

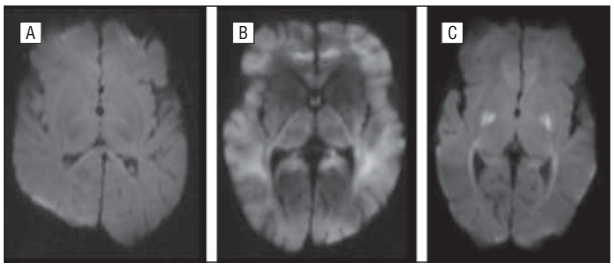

Figure 3. Appearance of hypoxic-ischemic encephalopathy on axial diffusion-weighted magnetic resonance imaging. A, A normal brain in a term newborn with no areas of restricted diffusion. B, Severely restricted diffusion in the basal ganglia and thalami, posterior limb of the internal capsule, and white matter. C, Focal restricted diffusion in the putamen and optic radiations.

dependent predictors of outcome. Again, results are presented as ORs (95% CIs). Finally, we calculated the sensitivity, specificity, and positive and negative predictive values for each MRI variable in predicting 2-year outcomes, presented with 95% CIs.

RESULTS

Two hundred twenty-one neonates were recruited into the ICE trial; 177 underwent MRI, of which images for 128 were made available for independent assessment for this substudy, including 127 images suitable for T1- and T2-weighted analysis and 126 for DWI and ADC analyses. No congenital brain malformations were noted on MRI in any of the participants. Baseline characteristics were similar for the participants in this substudy compared with participants in the ICE study without MRIs available (results not shown).

Table 1 summarizes the patient characteristics of this substudy. Sixty-six newborns underwent treatment with hypothermia and 61 with normothermia. All baseline characteristics were similar between the groups in this substudy. The differences in mortality and the 2-year outcome of death or major disability between the groups were not statistically significant in this substudy, in contrast to the results for the study overall.

Table 2 summarizes the MRI abnormalities present by treatment group. Fewer newborns had moderate/severe white matter and cortical gray matter abnormalities on T1- and T2-weighted MRI in the hypothermia-treated compared with the normothermia-treated newborns (OR for white matter, 0.28 [95% CI, 0.09-0.82]; OR for gray matter, 0.41 [0.17-1.00]). Although fewer abnormalities of the PLIC were detected on T1- and T2-weighted MRI in the hypothermia-treated group, this difference did not

reach statistical significance. We found a trend to reduction in diffusion abnormalities in the PLIC, BGT, white matter, and cortical gray matter in newborns treated with hypothermia compared with normothermia, but this difference also did not reach statistical significance.

All T1- and T2-weighted and diffusion MRI abnormalities were predictive of death or major sensorineural disability at 2 years of age (**Table 3**). There was little evidence of an interaction between hypothermia treatment and the prognostic utility of any of the MRI variables (all interaction, $P > .05$, where calculable). When age at MRI was included as a covariate, the prognostic utility of all T1- and T2-weighted and diffusion abnormalities remained unchanged (data not shown). Combining predictors into a single model for T1- and T2-weighted imaging found abnormal PLIC (OR, 4.10 [95% CI, 1.13-14.84; $P = .03$]) and moderate/severe BGT abnormalities (OR, 10.09 [3.19-31.85; $P < .001$]) were independent predictors of 2-year outcome. Similarly, abnormal PLIC (OR, 4.81 [95% CI, 1.40-16.60; $P = .01$]) and moderate/severe BGT abnormalities (OR, 9.38 [2.88-30.55; $P < .001$]) on diffusion MRI were independent predictors of 2-year outcome.

All T1- and T2-weighted and diffusion abnormalities had high sensitivity and negative predictive values as predictors for adverse outcome at 2 years of age (**Table 4**). Moderate to severe BGT abnormalities had the highest combined sensitivity and specificity (and positive and negative predictive values) for adverse outcome at 2 years for T1- and T2-weighted images and DWI.

Table 1. Participant Characteristics[a]

Characteristic	Treatment Groups: Hypothermia (n = 66)	Treatment Groups: Normothermia (n = 61)	*P* Value[b]
Male sex, No. (%)	35 (53)	38 (62)	.29
Gestational age, wk	38.9 (1.8)	38.9 (1.6)	.85
Birth weight, g	3318 (635)	3489 (597)	.12
10-min Apgar score, median (IQR)[c]	4.0 (2.5-5.0)	4.0 (3.0-5.0)	.57[d]
Severity of encephalopathy at assessment of eligibility for the ICE trial, No. (%)[e]			
Moderate	39 (59)	31 (51)	.77
Severe	14 (21)	14 (23)	
Cord or blood gas pH within 1 h of birth[f]	6.9 (0.2)	6.9 (0.2)	.82
Base excess, mEq/L[g]	–20.8 (7.9)	–19.2 (9.6)	.36
Clinical seizures, No. (%)	49 (74)	48 (79)	.35
Age at randomization, h	4.0 (1.3)	3.9 (1.2)	.53
Time of MRI, median (IQR), postnatal d	6 (3-7)	6 (4-8)	.89
Death, No. (%)			
For this substudy	14/66 (21)	17/61 (28)	.38
For the ICE trial	27/108 (25)	42/109 (39)	.03
Death or major disability at age 2 y, No./Total No. (%)[h]			
For this substudy	30/65 (46)	33/57 (58)	.20
For the ICE trial	55/107 (51)	67/101 (66)	.03

Abbreviations: ICE, Infant Cooling Evaluation; IQR, interquartile range; MRI, magnetic resonance imaging.
[a] Unless otherwise indicated, data are expressed as mean (SD).
[b] Calculated from *t* tests for continuous variables and χ^2 tests for categorical variables.
[c] Data were unavailable for 4 participants.
[d] Calculated from a Wilcoxon rank sum test.
[e] Data were unavailable for 1 participant in the normothermia group.
[f] Data were unavailable for 2 participants in the hypothermia group and 13 in the normothermia group.
[g] Data were unavailable for 13 participants in the hypothermia group and 17 in the normothermia group.
[h] Data were missing for 5 participants of this substudy and 9 in the ICE study.

COMMENT

The results from this substudy of a large, multicenter, randomized controlled trial of whole-body hypothermia in neonates with HIE demonstrate that brain injury in the white matter and cortical gray matter, identified on conventional T1- and T2-weighted MRI, was reduced in newborns who received hypothermia treatment compared with those who received normothermia treatment. We also found a trend toward reduced abnormalities in the PLIC in hypothermia-treated newborns, although with little evidence of an effect of therapeutic hypothermia on injury within the BGT.

A reduction in the extent of brain injury on conventional T1- and T2-weighted MRI with hypothermia treatment has been previously described,[12,17,18] although findings regarding the regions of the brain protected by hypothermia treatment have varied. One study reported a reduction in BGT lesions,[17] whereas another reported a reduction in cortical gray matter abnormalities.[18] A more recent report from the TOBY trial found that hypothermia treatment was associated with a reduction in abnormalities in several brain regions, including the BGT, PLIC, and white matter.[12] In the present study, the proportion of newborns with moderate/severe white matter and cortical gray matter abnormalities on conventional MRI was reduced with hypothermia treatment, with a trend for a reduction in PLIC abnormalities. However, we found little evidence of a difference in BGT abnormalities between the groups. Lesions of the BGT have been recently reported to be strongly associated with motor outcomes in early childhood.[10] The TOBY trial found a reduction in cerebral palsy in newborns who received hypothermia,[4] but this was not seen in the ICE trial; instead, mortality and the combined outcome of death or major disability were reduced, but the rate of cerebral palsy was similar between groups.[7] Moreover, the 2-year outcomes in this substudy were similar in neonates treated with hypothermia compared with those allocated to normothermia. The difference in motor outcomes between the TOBY and ICE randomized trials may explain why a reduction in MRI brain abnormalities was seen in different regions in the hypothermia- compared with normothermia-treated groups. These differences in neurological outcomes and underlying patterns of brain injury may also reflect the difference in the nature of the recruited population, in particular, variation in the inclusion criteria. In addition, other factors, including the different MR se-

Table 2. MRI Abnormalities in Hypothermia-Treated Group vs Normothermia-Treated Group

	Treatment Group, No. (%) of Participants			
	Hypothermia (n = 66)	Normothermia (n = 61)	OR (95% CI)[a]	*P* Value[a]
T1- and T2-weighted abnormalities (n = 127)				
PLIC score	14 (21)	22 (36)	0.48 (0.22-1.05)	.07
Moderate/severe in BGT	23 (35)	22 (36)	0.95 (0.46-1.96)	.89
Moderate/severe in white matter	5 (8)	14 (23)	0.28 (0.09-0.82)	.02
Moderate/severe in cortical gray matter	9 (14)	17 (28)	0.41 (0.17-1.00)	.05
Diffusion abnormalities (n = 126)				
PLIC score	13 (20)	18 (30)	0.60 (0.26-1.36)	.22
Moderate/severe in BGT	17 (26)	20 (33)	0.73 (0.34-1.57)	.42
Moderate/severe in white matter	7 (11)	13 (21)	0.45 (0.16-1.21)	.11
Moderate/severe in cortical gray matter	10 (15)	16 (26)	0.51 (0.21-1.24)	.14

Abbreviations: BGT, basal ganglia and thalami; MRI, magnetic resonance imaging; OR, odds ratio; PLIC, posterior limb of the internal capsule.
[a] Calculated from separate logistic regression models for T1- and T2-weighted and diffusion variables with treatment group as a predictor.

Table 3. MRI Characteristics as Predictors of Death or Major Disability at Age 2 Years

	Death/Disability at Age 2 y, No. (%)				
	Normal MRI Score	Abnormal MRI Score	OR (95% CI)[a]	*P* Value	*P* Value for Interaction[b]
T1- and T2-weighted abnormalities (n = 122)					
PLIC score	33/88 (38)	30/34 (88)	12.08 (3.89-37.52)	<.001	.33
BGT score	25/79 (32)	38/43 (88)	17.56 (6.05-51.02)	<.001	.50
White matter score	47/103 (46)	16/19 (84)	5.92 (1.59-21.96)	.008	NA
Cortical gray matter score	40/96 (42)	23/26 (88)	10.27 (2.86-36.91)	<.001	.83
Diffusion abnormalities (n = 121)					
PLIC score	36/91 (40)	26/30 (87)	9.62 (3.09-29.97)	<.001	NA
BGT score	30/85 (35)	32/36 (89)	14.54 (4.67-45.25)	<.001	.42
White matter score	45/101 (45)	17/20 (85)	6.62 (1.81-2419)	.004	NA
Cortical gray matter score	39/95 (41)	23/26 (88)	10.50 (2.83-37.55)	<.001	NA

Abbreviations: BGT, basal ganglia and thalami; MRI, magnetic resonance imaging; NA, not available; OR, odds ratio; PLIC, posterior limb of the internal capsule.
[a] Results from separate regression models for death/disability for each T1- and T2-weighted and diffusion predictor adjusted for treatment group.
[b] A number of the interactions were not available because of a zero cell in the cross-tabulation of the predictor and outcome within one or both of the treatment groups.

quences used and the timing of MRI, may account for the different findings in the present study and the TOBY study. The median age at the time of imaging in the present study was 6 days, which is earlier than that in the previous report from the TOBY substudy (median age at the time of the scan, 8 days).[12] Nonetheless, reductions in injury in brain regions reported in both MRI studies are similar to those reported in experimental models of perinatal HI. Reduction in histologic injury in the cortex, deep gray matter, hippocampus, brainstem, and cerebellum has been previously described in rodents, piglets, and sheep.[19-21]

Abnormalities of the BGT and PLIC on conventional MRI have been shown to be strongly correlated in previous studies, most of which have had the MRIs performed after the first postnatal week.[10,12] In the group of newborns in our substudy with the combination of moderate/severe BGT abnormalities and a normal PLIC, the median timing of MRI was 4 days after birth. Because the cerebral abnormalities after HIE are evolving during this early period, the BGT may have been established before the PLIC abnormalities became apparent. This finding may have been exaggerated in the hypothermia-treated group because of the temporal effects of evolution of MRI cerebral abnormalities related to hypothermia.

In the present study, we found that moderate to severe brain lesions in the PLIC, BGT, white matter, and cortical gray matter on conventional T1- and T2-weighted and diffusion MRI were all prognostic of poor outcome at 2 years of age. Moreover, there was little evidence that the prognostic utility of MRI was altered by hypothermia treatment. This finding is important for clinicians because hypothermia is now widely used to treat moderate to severe HIE. Of the MR lesions considered, abnormalities of the PLIC and BGT on conventional and diffusion MRI were independent predictors of death or major disability at 2 years of age, with sensitivities in the range of 87% to 89% and high negative predictive values of approximately 93%. As alluded to earlier, given the conspicuity and timing of diffusion changes in the brain after HIE, significant reliance is placed on this sequence for clinical interpretation in the first week after birth. Thus, the finding that diffusion abnormalities on MRI at the end of the first week after birth are predictive

Table 4. MRI Variables as a Diagnostic Tool for Predicting Death or Major Disability at Age 2 Years

	Variable, % (95% CI)			
	Sensitivity	Specificity	PPV	NPV
T1- and T2-weighted abnormalities (n = 122)				
PLIC score	48 (35-61)	93 (84-98)	88 (73-97)	63 (52-73)
Moderate/severe in BGT	60 (47-72)	92 (81-97)	88 (75-96)	68 (57-78)
Moderate/severe in white matter	25 (15-38)	95 (86-99)	84 (60-97)	54 (44-64)
Moderate/severe in cortical gray matter	37 (25-50)	95 (86-99)	89 (70-98)	58 (48-68)
Diffusion abnormalities (n = 121)				
PLIC score	42 (30-55)	93 (84-98)	87 (69-96)	60 (50-71)
Moderate/severe in BGT	52 (39-65)	93 (84-98)	89 (74-97)	65 (54-75)
Moderate/severe in white matter	27 (17-40)	95 (86-99)	85 (62-97)	55 (45-63)
Moderate/severe in cortical gray matter	37 (25-50)	95 (86-99)	89 (70-98)	59 (48-69)

Abbreviations: BGT, basal ganglia and thalami; MRI, magnetic resonance imaging; NPV, negative predictive value; PLIC, posterior limb of the internal capsule; PPV, positive predictive value.

of death or significant sensorineural disability at 2 years is of clinical and practical importance.

Concerns have been raised about the possibility of hypothermia treatment affecting the time course of lesion evolution on MRI, especially with diffusion restriction. Given that hypothermia seems to affect lesion evolution, this finding may have potential implications on the optimal timing of MRI for prognostic purposes. Previous recommendations are that MRI be performed at the end of the first postnatal week when acute changes have occurred but before the evolution of brain atrophy[22,23]; another study reported that MRIs performed at a median of 8 days were prognostic of outcome.[12] Although the present study could not address the question of optimal timing of MRI for prognostication in hypothermia-treated newborns with HIE, we demonstrated that MRIs performed at a median age of 6 days are prognostic of death or major sensorineural disability at 2 years. When age at MRI was included as a covariate in our analysis, the prognostic utility of conventional and diffusion MRI remained unaltered.

This study has several strengths. The sample size is relatively large and constitutes a representative subgroup of a large, multicenter, randomized controlled trial; therefore, the results are likely to be applicable to many tertiary neonatal centers that administer hypothermia treatment to term newborns with HIE. The MRI classification system used is simple, has a high interrater reliability,[12] and can be practically used in the clinical setting. However, for individualized and more refined prognostication of outcome, a more detailed MRI appraisal of abnormalities may be required. In addition, we have reported on MRI abnormalities and the prognostic utility of diffusion imaging, a widely used sequence in newborn HIE neuroimaging protocols.

However, we also acknowledge some limitations. Not all newborns in the ICE trial underwent MRI, and not all MRIs were made available for this substudy, although the clinical characteristics of the newborns in this substudy were similar to those of participants in the larger ICE trial. Because higher rates of death were found in the ICE trial compared with this substudy, the most severely affected neonates may not have had MRI examinations performed before redirection to palliative care, which would have been in the first few days after birth. There were also variations within the sequence protocol between centers within the ICE trial, which may have affected the interpretation of more subtle changes in the MRIs.

In summary, the reduction in brain injury in the hypothermia-treated group compared with the normothermia-treated group found in this study further supports hypothermia as a treatment for moderate to severe HIE in terms of reducing the incidence of white and cortical gray matter abnormality. Moreover, these results have shown that conventional and diffusion MRI of the brain are important biomarkers of long-term outcome in newborns with HIE, with or without hypothermia treatment.

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