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Neonatal Magnetic Resonance Imaging Pattern of Brain Injury as a Biomarker of Childhood Outcomes following a Trial of Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy

Seetha Shankaran, MD¹, Scott A. McDonald, BS², Abbot R. Laptook, MD³, Susan R. Hintz, MD⁴, Patrick D. Barnes, MD⁵, Abhik Das, PhD², Athina Pappas, MD¹, and Rosemary D. Higgins, MD^{5,*} on behalf of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

¹Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI

²Biostatistics and Epidemiology Division, Research Triangle Institute, International, Research Triangle Park, NC

³Department of Pediatrics, Women and Infant's Hospital, Brown University, Providence, RI

⁴Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA

⁵Department of Radiology, Stanford University School of Medicine, Palo Alto, CA

Abstract

Objective—To examine the ability of magnetic resonance imaging (MRI) patterns of neonatal brain injury defined by the National Institute of Child Health and Human Development Neonatal Research Network to predict death or IQ at 6–7 years of age following hypothermia for neonatal encephalopathy.

Study design—Out of 208 participants, 124 had MRI and primary outcome (death or IQ <70) data. The relationship between injury pattern and outcome was assessed.

Results—Death or IQ <70 occurred in 4 of 50 (8%) of children with pattern 0 (normal MRI), 1 of 6 (17%) with 1A (minimal cerebral lesions), 1 of 4 (25%) with 1B (extensive cerebral lesions), 3 of 8 (38%) with 2A (basal ganglia thalamic, anterior or posterior limb of internal capsule, or watershed infarction), 32 of 49 (65%) with 2B (2A with cerebral lesions), and 7 of 7 (100%) with pattern 3 (hemispheric devastation), $P < .001$; this association was also seen within hypothermia and control subgroups. IQ was 90 ± 13 among the 46 children with a normal MRI and 69 ± 25 among the 50 children with an abnormal MRI. In childhood, for a normal outcome, a normal neonatal MRI had a sensitivity of 61%, specificity of 92%, a positive predictive value of 92%, and

Reprint requests: Seetha Shankaran, MD, Department of Pediatrics, Wayne State University School of Medicine, Children's Hospital of Michigan, 3901 Beaubien Blvd, Detroit, MI 48201. sshankar@med.wayne.edu.

*List of members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network is available at www.jpeds.com (Appendix).

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a negative predictive value of 59%; for death or IQ <70, the 2B and 3 pattern combined had a sensitivity of 81%, specificity of 78%, positive predictive value of 70%, and a negative predictive value of 87%.

Conclusions—The Neonatal Research Network MRI pattern of neonatal brain injury is a biomarker of neurodevelopmental outcome at 6–7 years of age.

Brain injury in neonates following hypoxic-ischemic encephalopathy (HIE) prior to the introduction of neuroprotection with hypothermia was generally described in magnetic resonance imaging (MRI) studies as either white matter (WM) injury extending to the cortical areas or deep gray nuclei injury in the basal ganglia or thalamus (BGT), or involvement in both areas.^{1–6} In childhood, these areas of brain injury were associated with cognitive delays and motor impairment.^{3,7–9}

Hypothermia initiated within 6 hours of age at 33°C–34°C and continued for 72 hours decreases death or disability at 18–24 months of age or increases the number of normal survivors.^{10–15} Rutherford et al¹² have reported MRI results of the Total Body Hypothermia for Neonatal Encephalopathy trial demonstrating a reduction in lesions in the BGT, WM, and the abnormal posterior limb of the internal capsule (PLIC) among cooled infants with a predictive ability of death or disability of 84% in the cooled group and 81% in the noncooled group.¹⁶ The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) investigators described a decrease in areas of infarction in the watershed (WS) area among infants in the hypothermia group and described an MRI pattern of brain injury that correlated with death or disability at 18 months of age.¹⁷ The Infant Cooling Evaluation trial group noted WM injury was decreased among cooled infants compared with the noncooled group, and PLIC and BGT injury were associated with death or disability at 24 months of age.¹⁸ Thus, the neonatal MRI assessment of brain injury appears to be a biomarker of 18- to 24-month outcome following hypothermia for neonatal HIE.

The 6- to 7-year outcomes of trial participants in the NICHD trial and the Total Body Hypothermia for Neonatal Encephalopathy trial have recently been reported showing decreased mortality and better neurodevelopmental outcome in childhood in the cooled group.^{19,20} We wished to examine whether the NICHD MRI pattern of neonatal brain injury could be used as a biomarker of childhood outcome following neonatal HIE. The hypothesis of this study was that the NICHD NRN MRI pattern of neonatal brain injury would be associated with childhood neurocognitive outcome among participants in the trial of hypothermia for neonatal HIE ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00005772): NCT00005772). The objective of our study was to examine the association between neonatal brain injury pattern and outcome of death or IQ <70 at 6–7 years of age (primary outcome). Our secondary objective was to examine the association of brain injury pattern with level of disability and with child health and emotional outcome.

Methods

Term infants were eligible if they had severe acidosis or birth resuscitation following an acute perinatal event and moderate or severe encephalopathy within 6 hours of birth. After

informed consent was obtained from a parent, infants were randomly assigned by telephone by the data-coordinating center (RTI International, Research Triangle Park, North Carolina) to whole body hypothermia at 33.5°C for 72 hours or usual intensive care. The cranial imaging included an MRI to be performed at 44 weeks postmenstrual age or when clinically feasible; studies performed after 60 days of age were excluded. T1- and T2-weighted sequences with 1.5 or 3.0 Tesla conventional images were obtained. The data collection form captured areas of brain injury,^{1,2} as well as detailed information on size (minimal or more extensive), type (cystic, nonhemorrhagic, mineralization, gliosis), and location of signal abnormalities in the following regions: cerebral hemispheres, intraventricular areas, cerebellum, BGT, anterior limb of the internal capsule (ALIC) and PLIC, corona radiata, hippocampus, optic chiasm, and extra-axial areas. Areas of WS infarction, cerebral atrophy, and ventricular enlargement were also noted.¹⁷ The MRI scans were read by the central reader (P.B.), and the hypothermia study subcommittee created the following injury pattern: 0, normal MRI; 1A, minimal cerebral lesions only with no involvement of BGT, ALIC, PLIC, or WS infarction; 1B, more extensive cerebral lesions only with no involvement of BGT, ALIC, PLIC, or WS infarction; 2A, any BGT, ALIC, PLIC, or WS infarction noted without any other cerebral lesions; 2B, involvement of either BGT, ALIC, PLIC, or area of infarction and additional cerebral lesions; and 3, cerebral hemispheric devastation.¹⁷ All infants were coded on the pattern of injury without knowledge of treatment intervention status (Figure; available at www.jpeds.com). The protocol was approved by the institutional review board of the NRN centers.

At ages 6–7 years, all children had neurocognitive evaluations by trained and certified examiners unaware of neonatal treatment status. The follow-up visits occurred between August 2006 and August 2010. The primary outcome was death or full-scale IQ <70, with the IQ measured using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) III for children age under 7 years and 3 months or the Wechsler Intelligence Scale for Children IV for older children (normal mean $\pm$ SD, 100 $\pm$ 5). Children who could not be tested because of severe developmental delay were assigned an IQ score of 39. Higher cognitive function (attention and executive function and visuospatial processing) was evaluated among children who could be evaluated, using the Developmental Neuropsychological Assessment on which a score of 100 $\pm$ 15 is normal. Disability was categorized to 4 levels; severe disability was defined as an IQ <55 (3 SD below the mean) or a Gross Motor Function Classification System²¹ (GMFCS) level IV or V or bilateral blindness; moderate disability was categorized as an IQ between 55 and 69 (2–3 SD below the mean), or GMFCS level III, deafness (with or without amplification) or refractory epilepsy; mild disability was defined as an IQ between 70 and 84 or GMFCS level I or II. A normal outcome was categorized as an IQ above 85 without any neurological abnormality, sensory deficit, or epilepsy. Cerebral palsy (CP) was categorized on the basis of the Surveillance of Cerebral Palsy in Europe Network decision tree as ataxic, spastic unilateral, spastic bilateral, dystonic, choreoathetotic, or mixed/unclassifiable.²² All nondisabled children were assessed for every day motor-function (ability to walk), complex-motor function (heel-to-toe test, ability to hop, stand on one foot, and Romberg test), and fine motor function (finger-nose test, rapid alternation of hands, thumb-index finger apposition, thumb-four finger apposition sequentially, heel-to-shin test, and foot-tapping).

The Child Health Questionnaire, which has good psychometric properties for children with or without CP, was completed by the parents to evaluate the physical, emotional, and social well-being of the study children and to assess the effect of the child's health on the parents.²³ The sections on child's global health, you and your family, and self-esteem were used for this study.

Statistical Analyses

The study cohort included participants with neonatal MRI and primary outcome data at 6–7 years of age. The maternal and neonatal characteristics of the children who were part of the study cohort and those who were not in the study were compared, as were the clinical characteristics of those who had a neonatal MRI ≤ 7 days vs >7 days, to evaluate for bias using Fisher exact test for categorical variables and t tests for continuous variables. The relationship between the MRI patterns of injury and the primary outcome was assessed by Cochran-Armitage trend tests with the NICHD pattern of injury used as a 6-level variable (0, 1A, 1B, 2A, 2B, and 3). The relationship between the MRI patterns of injury and the level of disability among survivors was assessed by Fisher exact test, after collapsing the NICHD pattern of injury into 4 levels (0, 1, 2, and 3). Adjustment for treatment group and maternal education was not possible when evaluating the association between the neonatal MRI injury pattern and the 6- to 7-year outcome as the models did not converge. Linear regression was used to assess the adjusted mean differences of outcomes between normal and abnormal MRI groups, after adjustment for treatment, maternal education, and age of MRI. The relationships between specific areas of brain injury and IQ at 6–7 years were assessed using Fisher exact test or Cochran-Armitage trend test (ALIC, PLIC, and WS area); the relationships between normal/abnormal MRI and parent assessment outcomes were assessed using Cochran-Armitage trend tests. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for a normal neonatal MRI and a normal childhood outcome and those of pattern 2B and 3 combined (because numbers were small and these 2 patterns reflect major injury), and death or IQ <70 were assessed.

Results

The trial recruited 208 subjects between July 2000 and May 2003 in the 15 participating NICHD NRN centers. Neonatal brain MRI studies were performed on 136 of 208 trial participants at 15.3 ± 12.3 days of life. The neonates who did not have MRI studies included the following: (1) among the 47 who died in the neonatal intensive care unit, only 4 had MRI studies, and 2 were obtained after 60 days and 2 were of inadequate quality; and (2) of the 25 neonates who survived to neonatal intensive care unit discharge without requisite MRI, 14 did not have MRI studies performed, 5 underwent MRI after 60 days of age, and 6 neonates had MRIs that were of inadequate quality. Six- to 7-year outcome data and MRI data were available on 124 of the 136 children; among the 12 children with no data at 6–7 years of age, 10 had neonatal MRI studies that were normal, 1 child had a score of 2B, and the other had a score of 3. The 124 children with both MRI and 6- to 7-year outcome data comprise the cohort evaluated in this report.

The maternal and neonatal characteristics (at random assignment into study intervention at <6 hours of age) were comparable between the 124 children evaluated in this report and the 84 not in this report, except that mothers of children in this report were younger and had a higher rate of cord prolapse. In addition, fewer children received continued resuscitation at 10 minutes of age compared with children not in this report (Table I; available at www.jpeds.com). Twenty-four infants had MRI evaluations prior to 7 days, 10 on day 7, 49 between 8 and 14 days, and 41 between 14 and 58 days of age. The baseline maternal and neonatal characteristics were compared between the 34 infants who had the MRI studies 7 days of age and the 90 infants who had the studies performed after 7 days of age (Table II; available at www.jpeds.com). The 2 groups were comparable except that 88% of the infants in the 7 days were intubated in the delivery room compared with 99% in the group with the later MRIs ($P < .05$).

The primary outcome of death or IQ <70 occurred among 4 of 50 (8%) children with a normal MRI, 1 of 6 (17%) with 1A pattern of MRI injury, 1 of 4 (25%) with 1B pattern, 3 of 8 (38%) with 2A pattern, 32 of 49 (65%) with 2B classification, and all 7 children with pattern 3 (Table III). Among the 4 children whose MRIs were normal and who had the primary outcome, 2 died. One of these 2 had normal MRI at 8 days and died of viral pneumonia at 47 days of age, and the other infant had a normal MRI at 28 days and died after hospital discharge and prior to the 18-month visit (information on the age and cause of death are not available). The other 2 children had normal MRI studies at 7 and 23 days of age; at 6–7 years of age their IQ scores were 63 and 69, respectively.

To evaluate the impact of timing of MRI on the pattern of injury and outcome, a linear regression was evaluated for IQ, adjusting for the pattern of injury (6 levels), age at MRI (<7 days vs >7 days), treatment group, maternal education (<high school), and an interaction term between NICHD pattern and age of MRI. The NICHD pattern ($P < .0001$) and maternal education ($P = .02$) were significant in this model; the interaction term ($P = .22$), and age at MRI ($P = .15$) and treatment group were not significant.

The association between pattern of injury and primary outcome was significant ($P < .0001$, Cochran-Armitage trend test; Table III). The relationship of the injury pattern and level of disability among the 96 surviving children was significant when the pattern of injury was collapsed into 4 levels (0, 1, 2, and 3) because numbers were small in many cells, $P < .0001$ (Fisher exact test). Eight children did not have level of disability assessed. When outcome was assessed by treatment group (hypothermia, control), increasing severity on the MRI pattern of injury was associated with greater frequency of primary outcome in both treatment groups ($P < .0001$, Cochran-Armitage trend test), and the pattern of injury (collapsed into 4 levels) was associated with increasing level of disability at 6–7 years of age among surviving children (cooled infants, $P = .02$, control infants $P = .004$; both from Fisher exact test). The sensitivity, specificity, PPV, and NPV of an abnormal neonatal MRI for outcome of death or IQ <70 were 77%, 85%, 71%, and 89%, respectively, in the hypothermia group and 85%, 66%, 69%, and 83%, respectively, in the control group. These indices were similar in the cooled and control groups. We acknowledge the numbers are small in the groups assessed.

As a biomarker for a normal outcome at 6–7 years, a normal neonatal MRI (pattern 0) had a sensitivity of 61% (46/76), a specificity of 92% (44/48), a PPV of 92% (46/50), and a NPV of 59% (44/74). The predictive ability for a pattern of 2B and 3 combined for death or IQ <70 at 6–7 years had a sensitivity of 81% (39/48), specificity of 78% (59/76), PPV of 70% (39/56), and NPV of 87% (59/68).

The relationship of neonatal MRI and cognitive and motor outcome at 6–7 years of age following adjustment for treatment and maternal education is presented in Table IV. The IQ score was significantly higher among infants with the normal MRI ($n = 46$, $IQ\ 90 \pm 13$) compared with children with an abnormal MRI ($n = 50$, $IQ\ 69 \pm 25$, $P < .0001$). Among the children evaluated with the WPPSI ($n = 84$), the subscales of the verbal IQ, performance IQ, and the processing speed score were higher among the children with the normal MRI ($n = 38$) compared with those with an abnormal MRI ($n = 46$). Among the subset of children evaluated for attention executive ($n = 68$) and visuospatial scores ($n = 75$) using the Developmental Neuropsychological Assessment, no differences were noted between those with normal and abnormal neonatal MRI. The GMFCS level of disability and the Bimanual Motor Function level among children with CP (all in the abnormal MRI group) are also noted in Table IV.

When the IQ score was examined with the interaction term (MRI*treatment) included, normal vs abnormal MRI was still significant for outcome ($P < .0001$), but treatment group and interaction term were not significant. The model was also evaluated for IQ among children with normal MRI. Treatment group was not significant in this analysis.

Specific areas of brain injury and outcome among children with an IQ ≥ 70 compared with children whose IQ was <70 are noted in Table V. A higher frequency of IQ <70 was found with any injury noted in the cerebral areas (whether in the frontal, temporal, parietal, or occipital), BGT, caudate nucleus, ALIC, or PLIC. More children with IQ <70 had extensive infarction and hemispheric injury, and an enlarged subarachnoid space, although only 3 children had this type of injury.

There were 5 children with cognitive impairment (IQ <70) without CP; 2 had normal MRI, 1 child had BGT injury and equivocal ALIC, PLIC, and cerebral abnormalities in the frontal, temporal, parietal, and occipital areas; 1 child had frontal WM scarring/gliosis; and the remaining child had hemorrhage in the frontal, temporal, parietal, and occipital areas.

The type of CP among 19 of 23 children evaluated at the 6- to 7-year visit was spastic bilateral in 12, spastic unilateral in 1, dystonic in 3, choreoathetotic in 2, and ataxic in 1. The remaining 4 children had CP per the medical chart but did not attend the follow-up study visit. Because of small numbers, no exploratory analysis was performed to evaluate association with site of brain injury and type of CP.²⁴

Among 40 nondisabled survivors (26 with normal MRI, 14 with pattern 1 through 2B, and none had pattern 3), there was no association between injury pattern and abnormalities in every day motor function, gross motor function, or fine motor function (P value for no abnormality vs any abnormality = 0.68, data not shown).

The relationship of neonatal MRI and parental assessment of outcome is noted in Table VI. A normal neonatal MRI was associated with more parents who believed their child was in excellent or very good health. A normal neonatal MRI was also associated with more parents who were not worried about their child's emotional well-being or behavior. The parents' report of the child's self-esteem, however, was not different between children with a normal or abnormal neonatal MRI.

Discussion

We have demonstrated that the NICHD MRI pattern of neonatal brain injury is a marker of outcome at 6–7 years of age among neonates undergoing whole-body hypothermia or normothermia for neonatal HIE. This is the first study that has evaluated the prognostic ability of an MRI obtained in the neonatal period to determine neurodevelopmental outcome in childhood, among both cooled and control group participants. In the present study, which comprised 60% of the original randomized controlled trial participants (124 of 208), we have demonstrated that the 2B and 3 pattern of neonatal brain injury has high predictive indices for the primary outcome of death or IQ <70 at 6–7 years of age, and a normal MRI was also predictive of a normal outcome. This study is an extension of our previous work describing a neonatal MRI injury pattern based on existing assessment systems^{1,2} but also included additional areas of injury including hemispheric devastation, a finding not reported by other investigators.¹⁷

The association of MRI assessment systems and outcome in infancy among 173 term neonates with encephalopathy was noted by Miller.⁵ The BGT pattern was associated with the most impaired motor and cognitive outcome at 30 months, and the WS predominant pattern had an intermediate outcome; none of the neonates with a normal MRI had functional motor deficits or abnormal cognitive score.

Evaluation at 5–6 years of age with the WPPSI, Movement Assessment Battery for Children, and the Touwen Examination has shown that children with normal neonatal MRI scans who were considered normal at 2 years ($n = 34$) had deficits in later childhood; 74% were normal, 24% had minor neurological dysfunction and perceptual-motor difficulties, and 3% had cognitive impairment.³ Among 64 children with no functional impairment at 4 years of age, an increasing severity of WS-distribution in the neonatal MRI was associated with more impaired language-related abilities on the WPPSI-Revised.⁸ Therefore, assessments of children at ages older than infancy and detailed assessment of those with normal neonatal MRIs appear warranted. In our study, of the 50 children who had a normal MRI in the neonatal period, 30% had mild disability, 13% had moderate disability, and none of the children had severe disability.

In our study, we noted IQ scores were significantly higher among children with a normal MRI compared with those with an abnormal MRI, following adjustment for treatment, maternal educational level, and age at MRI. The verbal, performance, and processing speed scores and subscales of the IQ were also higher among the children who were evaluated by the WPPSI. The IQ scores among the children with a normal MRI were within the normal range for age (100 ± 15). This is encouraging as infants in this report all had moderate or

severe HIE and follow-up studies of children with HIE prior to the hypothermia era have noted lower IQ scores among all children surviving neonatal encephalopathy.^{25–28} Lower executive function, language, memory, and sensorimotor perception have also been reported among children who survived neonatal encephalopathy and were able to undergo higher cognitive function evaluation. The attention, executive, and visuospatial scores evaluated among the subset of children who could be tested (88% with normal neonatal MRI and 42% with an abnormal neonatal MRI) were not significantly different. This could reflect the supportive care (and neuroprotection) currently administered to all neonates being treated for neonatal HIE.

The most common site of injury in the neonatal MRI (pattern 2B) in our study was injury to the BGT, ALIC, PLIC, or WS area with additional cerebral lesions (49 of 124 children, 39.5%). The primary outcome of death or IQ <70 occurred among 65% of children with this MRI pattern; among those with hemispheric devastation (pattern 3), primary outcome was 100%. Similar to other investigators, we found that children with lesions limited to the cerebral areas only had either no disability or mild disability, and those with BGT and cerebral lesions together either had outcomes predominated by death or survival with an IQ <70 and moderate or severe disability.^{3,9,29,30} We had very few infants with thinning of the corpus callosum, which may influence motor performance³¹ or hippocampal injury that may cause memory impairment.³²

The type of CP following neonatal encephalopathy may be related to site of brain injury. In a previous study of 17 children with BGT lesions, mild motor delay was seen with the mild pattern of BGT injury, purely dyskinetic CP was seen with the moderate pattern of BGT injury, purely spastic CP with the severe BGT pattern, and dyskinetic/spastic CP noted with all 3 patterns of BGT injury.²⁴ In our study, children with CP (all in the abnormal MRI group) had delays in both gross motor function and bimanual fine motor tasks. Because of small numbers, we did not evaluate for association of type of CP and BGT injury.

There has been debate about whether cognitive impairment without CP can occur among children with perinatal asphyxia.³³ In this report, we did find that 5 children had an IQ <70 without CP with moderate disability in 3 and severe disability in one, and disability level missing in 1 child.

In this report, we found that rating of the child's health as very good/excellent was higher, and less concern was expressed about the child's behavior among parents with children with a normal MRI compared with those with an abnormal MRI. Previous investigators have noted an increase in behavioral problems in childhood following neonatal encephalopathy.³⁴ We noted that the child's self-esteem was not different whether the children had a normal or abnormal MRI. Other investigators have also noted that parent report of quality of life of children with CP is not influenced by the severity of the disability.³⁵

The strengths of our study include the large number of children evaluated with neonatal MRI studies and the duration of follow-up to 6–7 years of age. All MRI studies were read by a central pediatric neuroradiologist, and analyses were adjusted for socioeconomic status. The limitations of our study were unavailable data on 84 of 208 trial participants and lack of

evaluation of diffusion-weighted imaging. In addition, the age in days when the scans were obtained varied between 4 and 58 days. However, we did evaluate baseline characteristics between those with early vs. later scans and did not find that the infants with later scans were sicker. It is also possible that the timing of imaging could result in false negative interpretation of the MRI when performed at <7 days without the use of diffusion-weighted imaging. This is important as the primary outcome occurred among 4 of 50 children with a normal neonatal MRI, 1 of 6 with a 1A pattern, and 1 of 4 with a 1B pattern. In spite of these limitations, we noted associations between the more severe areas of neonatal injury and death or IQ <70. Therefore, the NRN neonatal MRI injury pattern may serve as a biomarker of brain injury and, along with follow-up, may be useful to evaluate response to future neuroprotective strategies.

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Glossary

ALIC	Anterior limb of the internal capsule
BGT	Basal ganglia or thalamus
CP	Cerebral palsy
GMFCS	Gross Motor Function Classification System
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
NICHD	National Institute of Child Health and Human Development
NPV	Negative predictive value
NRN	Neonatal Research Network
PLIC	Posterior limb of the internal capsule
PPV	Positive predictive value
WM	White matter
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WS	Watershed

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Appendix

The following investigators are members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network, National Institutes of Health, Bethesda, MD:

Abhik Das (Data Coordinating Center Principal Investigator) and Scott A. McDonald (Data Coordinating Center Statistician) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis.

Whole-body Hypothermia Subcommittee: Seetha Shankaran, MD, Chair (Wayne State University, Detroit, MI); Richard A. Ehrenkranz, MD, Vice Chair (Yale University, New Haven, CT); Ronald N. Goldberg, MD (Duke University, Durham, NC); Abbot R. Laptook, MD (Brown University, Providence, RI); Jon E. Tyson, MD, MPH (University of Texas Health Science Center, Houston, TX); Michele C. Walsh, MD, MS (Case Western Reserve University, Cleveland, OH); Abhik Das, PhD (RTI International, Rockville, MD); Rosemary D. Higgins, MD (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD); Ellen C. Hale, RN, BS, CCRC (Emory University, Atlanta, GA); Karen J. Johnson, RN (University of Iowa, Iowa City, IA).

Extended Hypothermia Subcommittee: Seetha Shankaran, MD, Chair (Wayne State University, Detroit, MI); Richard A. Ehrenkranz, MD, Vice Chair (Yale University, New Haven, CT); Susan R. Hintz, MD, MS Epi (Stanford University, Stanford, CA); Athina Pappas, MD (Wayne State University, Detroit, MI); Jon E. Tyson, MD, MPH (University of Texas Health Science Center, Houston, TX); Betty R. Vohr, MD (Brown University, Providence, RI); Kimberly Yolton, PhD (Cincinnati Children's Hospital Medical Center, Cincinnati, OH); Abhik Das, PhD (RTI International, Rockville, MD); Rosemary D. Higgins, MD (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD); Rebecca Bara, RN, BSN (Wayne State University, Detroit, MI).

Figure.

A, NICHD NRN score = 0 (Term infants; normal T2(3T and 1.5T)). **B**, NICHD NRN score 1A with minimal cerebral lesions only (*arrow*) without any involvement of the basal ganglia, thalamus, ALIC, PLIC, or WS infarction. **C**, NICHD NRN score 1B with more extensive cerebral lesion without any BGT, ALIC, PLIC, or infarction. **D**, NICHD NRN score 2A: any BGT, ALIC, PLIC, or WS infarction without any other cerebral lesions. **E**, NICHD NRN score 2B: BGT, ALIC, PLIC, or WS infarction and cerebral lesions. **F**, NICHD NRN score 3: cerebral hemispheric devastation.

Table I

Maternal and neonatal characteristics of study cohort and those not in the cohort

Characteristics	Children in the cohort, n = 124	Children not in the cohort, n = 84
Maternal		
Race, no. (%)		
Black	38 (31%)	34 (40%)
White	49 (40%)	23 (27%)
Other	37 (30%)	27 (32%)
Maternal age (y) *	26.5 ± 5.7	28.5 ± 6.4
Married, no. (%)	74 (61%)	41 (50%)
Gravida, median	2	2
Parity, median no.	2	1
Maternal education <high school (%)	40 (34%)	22 (32%)
Complications of pregnancy, no. (%)		
Chronic hypertension	17 (14%)	9 (11%)
Antepartum hemorrhage	17 (14%)	13 (15%)
Thyroid disease	0 (0%)	2 (2%)
Diabetes	10 (8%)	7 (8%)
Intrapartum complications, no. (%)		
Fetal heart rate decelerations	93 (76%)	60 (71%)
Cord prolapse *	30 (24%)	7 (8%)
Uterine rupture	18 (15%)	11 (13%)
Maternal pyrexia	15 (12%)	6 (7%)
Shoulder dystocia	13 (11%)	7 (8%)
Maternal hemorrhage	9 (7%)	5 (6%)
Emergency cesarean delivery, no. (%)	90 (73%)	62 (74%)
Neonatal		
Age at randomization (h)	4.3 ± 1.3	4.3 ± 1.2
Outborn, no. (%)	57 (46%)	36 (43%)
Male sex, no. (%)	65 (52%)	52 (62%)
Apgar score at 5 min 5, no. (%)	111 (90%)	78 (93%)
Apgar score at 10 min 5, no. (%)	91 (79%)	63 (83%)
Birth weight (g)	3335 ± 568	3439 ± 711
Intubation in delivery room, no. (%)	119 (96%)	76 (90%)
Continued resuscitation at 10 min, no. (%) *	112 (90%)	83 (99%)
Time to spontaneous respiration 10 min, no. (%)	83 (70%)	57 (73%)
Cord blood pH	6.9 ± 0.2	6.8 ± 0.2
Base deficit mmol/L	18.5 ± 7.3	20.4 ± 8.4
Seizures, no. (%)	60 (48%)	34 (40%)
Moderate encephalopathy, no. (%)	85 (69%)	49 (59%)
Severe encephalopathy, no. (%)	39 (31%)	34 (41%)
Inotropic support, no. (%)	39 (31%)	20 (24%)

Characteristics	Children in the cohort, n = 124	Children not in the cohort, n = 84
Anticonvulsants, no. (%)	56 (48%)	27 (38%)

Plus-minus values are means $\pm$ SD. Percentages are based on the number of mothers or children for whom data was available. Because of rounding, not all percentages sum to 100.

* *P* values .05 from Fisher exact test or *t* test.

Table II

Maternal and neonatal characteristics of infants with early MRI (≤ 7 days) vs late MRI (>7 days)

Characteristics	MRI ≤ 7 d, N = 34	MRI >7d, N = 90
Maternal		
Race, no. (%)		
Black	12 (35%)	26 (29%)
White	10 (29%)	39 (43%)
Other	12 (35%)	25 (28%)
Maternal age (y)	26.1 ± 5.9	26.6 ± 5.7
Married, no. (%)	21 (62%)	53 (61%)
Gravida, median no.	2	2
Parity, median no.	2	2
Maternal education <high school (%)	11 (34%)	29 (34%)
Complications of pregnancy, no. (%)		
Chronic hypertension	6 (18%)	11 (12%)
Antepartum hemorrhage	3 (9%)	14 (16%)
Thyroid disease	0 (0%)	0 (0%)
Diabetes	2 (6%)	8 (9%)
Intrapartum complications, no. (%)		
Fetal heart rate decelerations	25 (74%)	68 (76%)
Cord prolapse	10 (29%)	20 (22%)
Uterine rupture	4 (12%)	14 (16%)
Maternal pyrexia	3 (9%)	12 (13%)
Shoulder dystocia	4 (12%)	9 (10%)
Maternal hemorrhage	2 (6%)	7 (8%)
Emergency cesarean delivery, no. (%)	25 (74%)	65 (72%)
Neonatal		
Age at randomization (h)	4.5 ± 1.2	4.2 ± 1.3
Outborn, no. (%)	17 (50%)	40 (44%)
Male sex, no. (%)	14 (41%)	51 (57%)
Apgar score at 5 min ≤ 5, no. (%)	31 (91%)	80 (90%)
Apgar score at 10 min ≤ 5, no. (%)	27 (84%)	64 (77%)
Birth weight (g)	3292 ± 499	3351 ± 594
Intubation in delivery room, no. (%) [*]	30 (88%)	89 (99%)
Continued resuscitation at 10 min, no. (%)	29 (85%)	83 (92%)
Time to spontaneous respiration ≥ 10 min, no. (%)	23 (70%)	60 (70%)
Cord blood pH	6.9 ± 0.2	6.8 ± 0.2
Base deficit mmol/L	16.2 ± 7.6	19.4 ± 7.0
Seizures, no. (%)	14 (41%)	46 (51%)
Moderate encephalopathy, no. (%)	27 (79%)	58 (64%)
Severe encephalopathy, no. (%)	7 (21%)	32 (36%)

Characteristics	MRI 7 d, N = 34	MRI >7d, N = 90
Inotropic support, no. (%)	10 (29%)	29 (32%)
Anticonvulsants, no. (%)	10 (32%)	46 (53%)
In-hospital mortality, no. (%)	4 (12%)	11 (12%)
Mortality by 6–7 y, no. (%)	5 (15%)	15 (17%)

Plus-minus values are means $\pm$ SD. Percentages are based on the number of mothers or children for whom data was available. Because of rounding, not all percentages sum to 100.

* P values .05 from Fisher exact test, t test, or median test.

Table III

Relationship of neonatal MRI and 6- to 7-year outcome

MRI NICHD score	Death or IQ <70	Among survivors *			
		Normal	Mild disability	Moderate disability	Severe disability
Entire cohort					
0 n = 50	4 (8%)	26 (57%)	14 (30%)	6 (13%)	0 (0%)
1A n = 6	1 (17%)	2 (40%)	3 (60%)	0 (0%)	0 (0%)
1B n = 4	1 (25%)	2 (50%)	0 (0%)	1 (25%)	1 (25%)
2A n = 8	3 (38%)	4 (67%)	0 (0%)	2 (33%)	0 (0%)
2B n = 49	32 (65%)	7 (21%)	8 (24%)	3 (9%)	16 (47%)
3 n = 7	7 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Total n = 124	48 (39%)	41 (43%)	25 (26%)	12 (13%)	18 (19%)
P value <.0001 [†]					
<.0001					
Among cooled infants					
0 n = 35	3 (9%)	16 (50%)	11 (34%)	5 (16%)	0 (0%)
1A n = 4	0 (0%)	2 (50%)	2 (50%)	0 (0%)	0 (0%)
1B n = 1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
2A n = 5	1 (20%)	3 (75%)	0 (0%)	1 (25%)	0 (0%)
2B n = 22	15 (68%)	4 (29%)	3 (21%)	1 (7%)	6 (43%)
3 n = 2	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total n = 69	22 (32%)	25 (45%)	16 (29%)	7 (13%)	7 (13%)
P value <.0001 [†]					
.02					
Among control infants					
0 n = 15	1 (7%)	10 (71%)	3 (21%)	1 (7%)	0 (0%)
1A n = 2	1 (50%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
1B n = 3	0 (0%)	2 (67%)	0 (0%)	1 (33%)	0 (0%)
2A n = 3	1 (50%)	1 (50%)	0 (0%)	1 (50%)	0 (0%)
2B n = 27	17 (63%)	3 (15%)	5 (25%)	2 (10%)	10 (50%)
3 n = 5	5 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Total n = 55	26 (47%)	16 (39%)	9 (22%)	5 (12%)	11 (27%)

Among survivors [*]					
MRI NICHD score	Death or IQ <70	Normal	Mild disability	Moderate disability	Severe disability
<i>P</i> value <.0001 [†]					.004

Percentages given are row percentages.

^{*} Eight infants (4 cooled and 4 control infants) who had primary outcome adjudicated did not have level of disability. For the analysis of disability among survivors, injury pattern collapsed into 4 levels; P value from Fisher exact test.

[†] P value for primary outcome from Cochran-Armitage trend test.

Table IV

Relationship of neonatal MRI, and cognitive and motor outcome at 6–7 years of age

Cognitive and motor outcomes	N	Normal MRI, N = 50	Abnormal MRI, N = 74	Adjusted P value*	Adjusted mean difference (95% CI)
WPPSI IQ total score	38	89.8 ± 13.0	68.1 ± 25.8	<.0001	23.6 (14.6, 32.7)
Verbal score	38	88.9 ± 14.8	69.1 ± 25.9	<.0001	21.6 (12.1, 31.2)
Performance score	38	93.3 ± 12.5	71.2 ± 27.7	<.0001	22.8 (13.0, 32.5)
Processing speed score	37	97.5 ± 15.0	68.7 ± 26.2	<.0001	29.8 (19.6, 40.1)
WISC full scale Composite score IQ	8	93.4 ± 13.2	82.8 ± 12.4	.33	17.3 (-21.0, 55.6)
Verbal comprehension	8	93.1 ± 22.0	77.5 ± 12.8	.34	24.5 (-31.8, 80.8)
Perceptual reasoning	8	98.0 ± 13.7	88.8 ± 10.6	.62	8.5 (-29.9, 46.9)
Working memory	8	93.9 ± 14.5	90.8 ± 13.5	.53	11.9 (-29.9, 53.6)
Processing speed	8	94.3 ± 15.4	92.5 ± 17.3	.99	0.3 (-44.9, 45.5)
IQ: WPPSI total and WISC composite score	46	90.4 ± 12.9	69.3 ± 25.3	<.0001	21.3 (13.2, 29.5)
NEPSY: attention-executive					
Sum of scaled scores	42	28.2 ± 6.0	26.9 ± 6.8	.72	0.5 (-2.5, 3.5)
Sum of core domain scores	42	95.6 ± 15.1	92.7 ± 15.3	.69	1.5 (-6.1, 9.1)
NEPSY: visuospatial					
Sum of scaled scores	44	19.7 ± 4.2	18.1 ± 5.7	.14	1.7 (-0.6, 3.9)
Sum of core domain scores	44	99.0 ± 12.5	94.4 ± 17.3	.15	4.9 (-1.9, 11.6)
GMFCS level 1–5 (CP only)	0	-	4.4 ± 1.0 Median = 5 (4, 5)	N/A	N/A
Bimanual fine motor level 1–5 (CP only)	0	-	4.3 ± 1.1 5 (3, 5)	N/A	N/A

N/A, not applicable; NEPSY, Developmental Neuropsychological Assessment; WISC, Wechsler Intelligence Scale for Children.

Data presented for children who were able to undergo testing (or assignment of scores as noted in the Methods section).

* Adjusted for treatment group, maternal educational level (measured at baseline if available; otherwise measured at 18 months), and age of MRI (WPPSI, WPPSI and WISC, NEPSY only).

Table V

Relationship of specific area of brain injury and IQ at 6–7 years

	IQ 70	IQ <70	IQ 70 vs IQ <70, <i>P</i> value
	N = 76	N = 28	
Cerebral lesions	25 (33%)	23 (82%)	<.0001
Frontal	18 (24%)	19 (68%)	<.0001
Temporal	15 (20%)	18 (64%)	<.0001
Parietal	19 (25%)	18 (64%)	.0004
Occipital	13 (17%)	18 (64%)	<.0001
BGT	18 (24%)	21 (75%)	<.0001
Putamen	17 (22%)	21 (75%)	<.0001
Globus pallidus/lenticular nucleus	10 (13%)	15 (54%)	<.0001
Caudate	2 (3%)	5 (18%)	.01
ALIC			<.0001*
Normal	57 (75%)	5 (19%)	
Equivocal	12 (16%)	7 (27%)	
Abnormal	7 (9%)	14 (54%)	
PLIC			<.0001*
Normal	57 (75%)	5 (19%)	
Equivocal	12 (16%)	7 (27%)	
Abnormal	7 (9%)	14 (54%)	
WS area			.002*
0 no infarction	70 (93%)	20 (71%)	
1 single focal infarction	0 (0%)	0 (0%)	
2 antr or post WM	0 (0%)	0 (0%)	
3 antr or post WS and WM	1 (1%)	1 (4%)	
4 antr or post WS	1 (1%)	0 (0%)	
5 More extensive	3 (4%)	7 (25%)	
Total hemispheric devastation	0 (0%)	3 (11%)	.02
Other			
Corona radiata	3 (4%)	3 (11%)	.34
Hippocampus	0 (0%)	2 (7%)	.07
Markedly thin CC	0 (0%)	1 (4%)	.27
Marked ventricular enlargement	0 (0%)	1 (4%)	.27
Cerebellar lesion	0 (0%)	2 (7%)	.07
WM scarring	13 (17%)	10 (37%)	.06
Cerebral atrophy	1 (1%)	3 (11%)	.06
Brain stem	0 (0%)	1 (4%)	.27
Enlarged subarachnoid space	0 (0%)	3 (12%)	.02

CC, corpus callosum; *antr*, anterior; *post*, posterior.*P* values from Fisher exact test or *Cochran-Armitage trend test, % are column percentages.

Table VI

Relationship of MRI abnormalities and parent assessment outcomes at 6–7 years of age

Variables	Normal MRI	Abnormal MRI	<i>P</i> value
Health *			.01
Excellent	28 (58%)	19 (37%)	
Very Good	11 (23%)	13 (25%)	
Good	8 (17)	12 (24%)	
Fair	1 (2%)	6 (12%)	
Poor	0 (0%)	1 (2%)	.44
Child's self-esteem [†]			
Very satisfied	37 (77%)	32 (71%)	
Somewhat satisfied	10 (21%)	11 (24%)	
Neither satisfied nor dissatisfied	1 (2%)	2 (4%)	
Emotional Impact on parents [‡]			.03
None at all	24 (50%)	18 (35%)	
A little bit	10 (21%)	10 (20%)	
Some	7 (15%)	7 (14%)	
Quite a bit	4 (8%)	5 (10%)	
A lot	3 (6%)	11 (22%)	

* Parental assessment of child health. Data were unavailable for 25 children. *P* value from Cochran-Armitage trend test.

[†] Parental assessment of child's satisfaction with his/her life. Data were unavailable for 31 children. *P* value from Cochran-Armitage trend test.

[‡] Parental assessment of worry caused by child's emotional well-being or behavior. Data were unavailable for 25 children. *P* value from Cochran-Armitage trend test.