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

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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 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. *(J Pediatr 2015;167:987-93)*.

Trial registration ClinicalTrials.gov: NCT00005772.

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 al[12] 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

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

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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: 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 ± SD, 100 ± 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 ± 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 System[21] (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