# Acute Perinatal Sentinel Events, Neonatal Brain Injury Pattern, and Outcome of Infants Undergoing a Trial of Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy

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Infants with perinatal sentinel events in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network Hypothermia for Encephalopathy Trial had more basal ganglia and thalamus lesions on brain magnetic resonance imaging but similar neurodevelopmental outcomes at 18 months of age than infants without perinatal sentinel events. Outcomes correlated with the neonatal magnetic resonance imaging findings. *(J Pediatr 2017;180:275-8).*

**Trial registration** ClinicalTrials.gov: NCT00005772.

Specific acute clinical events that occur close to the time of delivery or are the primary reason for delivery are called perinatal sentinel events (PSEs). Prior to the era of therapeutic hypothermia, PSEs that result in neonatal hypoxic-ischemic encephalopathy (HIE) have been associated with basal ganglia and thalamus (BGT) lesions and less frequently with watershed (WS) injury on a magnetic resonance imaging (MRI).[1] Hypothermia for neonatal encephalopathy is currently the standard of care[2] because therapy 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[3-6] and increases the number of normal survivors.[7,8] Following the initiation of hypothermia for neonatal encephalopathy, a recent single- center study noted that infants with a PSE had a higher mortality rate and more severe injury on brain MRI compared with infants without PSE.[9]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) described brain MRI findings among 136 of 208 participants in a randomized controlled trial (RCT) of hypothermia compared with usual intensive care among neonates with HIE.[10] These findings were found to correlate with death or survival with moderate or severe disability at 18 months of age[10] and with childhood outcome at 6-7 years of age.[11] Using the detailed information on PSE that is available in this trial database, we designed the present study to examine whether PSEs are associated with MRI findings that are linked to death or disability.

| | |
|---|---|
| ALIC | Anterior limbs of the internal capsule |
| BGT | Basal ganglia and thalamus |
| HIE | Hypoxic-ischemic encephalopathy |
| MRI | Magnetic resonance imaging |
| NICHD | National Institute of Child Health and Human Development |
| NRN | Neonatal Research Network |
| PLIC | Posterior limbs of the internal capsule |
| PSE | Perinatal sentinel event |
| RCT | Randomized controlled trial |
| WS | Watershed |

## Methods

The NICHD NRN Trial of whole-body hypothermia for neonatal encephalopathy recruited 208 subjects between July 2000 and May 2003 in the 15 participating centers (ClinicalTrials.gov: NCT00005772). Term infants were eligible if they had an umbilical cord or first pH within 1 hour of birth that was ≤7.0, or they required resuscitation following an acute perinatal event and had moderate or severe encephalopathy within 6 hours of birth. After informed consent was obtained from a parent, infants were randomly assigned to whole-body hypothermia at 33.5°C for 72 hours or usual intensive care. MRIs were performed at 44 weeks postmenstrual age or when clinically feasible, but within 60 days of age. T1- and T2-weighted sequences with 1.5 or 3.0 Tesla conventional images were obtained. The data collection form captured areas of injury and location of signal abnormalities as described in **Table I**. The MRI scans were read by a single central reader (P.B.), and the hypothermia study subcommittee created an injury pattern where each level reflected a greater involvement of brain injury: 0 = normal MRI; 1A = minimal cerebral lesions only with no involvement

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**Table I. MRI findings among study subjects by region and pattern of injury**

| MRI results | With PSE n = 84 | Without PSE n = 52 | *P* value |
|---|---|---|---|
| Normal | 38 (45%) | 22 (42%) | .86 |
| Abnormal | 46 (55%) | 30 (58%) | |
| Total hemispheric devastation | | | |
| Any | 4 (5%) | 4 (8%) | .48 |
| Cerebral lesions—no. (%) | 39 (46%) | 26 (50%) | .73 |
| Any frontal | 31 (79%) | 19 (73%) | .56 |
| Any temporal | 30 (77%) | 16 (62%) | .27 |
| Any parietal | 30 (77%) | 19 (73%) | .77 |
| Any occipital | 28 (72%) | 15 (58%) | .29 |
| BGT classification—no. (%)* | | | .03 |
| Normal | 46 (58%) | 32 (65%) | |
| Minimal | 4 (5%) | 6 (12%) | |
| Moderate | 17 (21%) | 2 (4%) | |
| Severe | 13 (16%) | 9 (18%) | |
| PLIC classification—no. (%)* | | | .70 |
| Normal | 45 (54%) | 29 (57%) | |
| Equivocal | 18 (22%) | 8 (16%) | |
| Abnormal | 20 (24%) | 14 (27%) | |
| ALIC—no. (%)* | | | .58 |
| Normal | 45 (54%) | 29 (57%) | |
| Equivocal | 19 (23%) | 8 (16%) | |
| Abnormal | 19 (23%) | 14 (27%) | |
| Watershed area* | | | .08 |
| 0 = no infarction | 72 (87%) | 40 (77%) | |
| 1 = single focal infarction | 0 (0%) | 0 (0%) | |
| 2 = anterior or posterior white matter | 2 (2%) | 0 (0%) | |
| 3 = anterior, posterior WS | 1 (1%) | 2 (4%) | |
| Cortex and white matter | | | |
| 4 = anterior and posterior WS | 2 (2%) | 0 (0%) | |
| 5 = more extensive cortical involvement beyond WS zones | 6 (7%) | 10 (19%) | |
| Cerebellar injury (any cerebellar lesion) | 3 (4%) | 2 (4%) | 1.00 |
| Brain stem injury | 3 (4%) | 3 (6%) | .67 |
| Medulla | 2 (67%) | 1 (33%) | 1.00 |
| Pons | 1 (33%) | 1 (33%) | 1.00 |
| Midbrain | 2 (67%) | 2 (67%) | 1.00 |
| Subarachnoid hemorrhage (extra-axial hemorrhage) | 3 (4%) | 0 (0%) | .29 |
| Ventricular dilation (moderate/marked) | 6 (7%) | 3 (6%) | 1.0 |
| Pattern of injury | | | |
| NICHD NRN: | | | .45 |
| 0 | 38 (45%) | 22 (42%) | |
| 1A | 2 (2%) | 4 (8%) | |
| 1B | 4 (5%) | 0 (0%) | |
| 2A | 5 (6%) | 3 (6%) | |
| 2B | 31 (37%) | 19 (37%) | |
| 3 | 4 (5%) | 4 (8%) | |

*BGT: 7 infants could not be classified, PLIC: 2 infants could not be classified, ALIC: 2 infants could not be classified, WS area: 1 infant could not be classified.

of the BGT, anterior or posterior limbs of the internal capsule (ALIC, PLIC), or WS infarction; 1B = more extensive cerebral lesions 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 = 2A and cerebral lesions; and 3 = cerebral hemispheric devastation.[10] All infants were coded on the pattern of injury without knowledge of treatment intervention status or outcome.

PSE in this study was defined as any of the following: umbilical cord mishap (either cord prolapsed, knotted, torn, ruptured, or compressed), uterine rupture, placental abruption, shoulder dystocia and major maternal hemorrhage, trauma, cardiorespiratory arrest, or seizures immediately preceding delivery. The primary outcome was death or moderate/severe disability at 18-22 months of age. Severe disability was defined as any of the following: Bayley Scales of Infant and Toddler Development version II[12] Mental Developmental Index <70, Gross Motor Function Classification System Level 3-5[13] reflecting moderate or severe cerebral palsy, deafness, or blindness despite amplification. Moderate disability was defined as a Mental Developmental Index score of 70-84 and any of the following: Gross Motor Function Classification System level 2, hearing impairment, or active seizures at 18 months. The outcome at 6-7 years of age (death or IQ assessed by the Wechsler Preschool and Primary Scale of Intelligence or the Wechsler Scale of Intelligence for Children) was assessed among children who had data on neonatal MRI and 6-7 years of age outcome.[11] The RCT protocol was approved by the institutional review board of the NRN centers.

### Statistical Analyses

The study cohort included participants with data on neonatal MRI and neurologic and developmental outcome at 18-22 months of age. Data was analyzed at RTI International with SAS v 9.4 (SAS Institute, Cary, North Carolina). The maternal and neonatal characteristics of the infants who were part of the study cohort and those who were not in the study (absent MRI or outcome) were compared to evaluate for bias using Fisher exact test for categorical variables and *t* tests for continuous variables. MRI findings by brain region were compared between infants with and without PSE using the Fisher exact test. The relationship between the neonatal MRI findings (pattern 0, 1A, 1B, 2A, 2B, 3) among infants with and without acute PSE, and the primary outcome and components of the primary outcome was assessed by Cochran-Armitage trend tests, with the NICHD NRN pattern of injury used as a 6-level variable (0, 1A, 1B, 2A, 2B, 3).[10] The impact of cooling therapy on brain injury among infants with and without PSE was also examined by treatment groups (hypothermia and control) with the Fisher exact test. For the 6-7 years of age outcomes, only comparisons of primary outcome (IQ <70) were evaluated between children with and without PSE. This study involved exploratory analyses of an existing data set, which limited the sample size. There are no corrections made for multiple comparisons. Statistical significance was considered as *P* values of <.05.

## Results

Of the 208 infants enrolled in the original RCT, 136 infants had a MRI, and 84 had a history of PSE (**Table I**).

Maternal characteristics were comparable between the group with PSE and without PSE except that antepartum hemorrhage was higher in the group with PSE. The neonatal characteristics at <6 hours of age were similar in the 2 groups except that 5- and 10-minute Apgar scores were lower, and rates of delivery room intubation were higher in the group with PSE compared with those without PSE (data not shown).

The MRI findings by region and pattern of injury in the groups with and without a PSE are noted in **Table I**. Infants