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OUTCOMES in CHILDHOOD FOLLOWING THERAPEUTIC HYPOTHERMIA for NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

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Abstract

In this chapter we review the childhood outcomes of neonates with birth depression and/or hypoxic-ischemic encephalopathy. The outcomes of these children prior to the era of hypothermia for neuroprotection will first be summarized, followed by discussion of results from randomized controlled trials of therapeutic hypothermia for neonatal hypoxic ischemic encephalopathy. The predictors of outcome in childhood following neonatal HIE using clinical and imaging biomarkers following hypothermia therapy will be described.

Childhood outcomes prior to era of hypothermia therapy

Prior to the era of therapeutic hypothermia, reports of the outcomes of children with acute perinatal asphyxia and/or neonatal encephalopathy have noted that among children with moderate encephalopathy the disability rate ranges from 6–21% and among children with severe encephalopathy ranges from 42–100%[1–5]. In a small single center study, among 28 outborn term infants born between 1980–82 with severe perinatal asphyxia and moderate or severe encephalopathy, multiorgan dysfunction involving pulmonary, central nervous system, renal, cardiac, metabolic, and hematological systems were noted[1]. The majority of neonates had more than 3 organ systems involved; 24 survived and all organ systems recovered except the central nervous system. At 5 years, 14 of 24 surviving children (58%) had a normal neurological examination, 9 had spastic quadriplegia and 1 had hemiplegia. Nine children had a cognitive index > 84, 3 scored between 68 and 83 and 12 scored< 67 on the McCarthy General Cognitive Index. Robertson et al reported on two regional cohorts (the first born 1974–79, the second 1982–86); term infants with moderate or severe encephalopathy who survived were followed to school age[2]. In both cohorts the children with moderate encephalopathy (n=84 and 97, respectively) had a disability rate of 21%, while those with severe encephalopathy (n=5 and 6, respectively) had a disability rate of 100%. The *non-disabled* children from both cohorts, all with moderate encephalopathy (66 and 64 respectively) who had assessment of intelligence quotient (IQ) at school-age (5.5 years) scored approximately 10 points lower than matched comparison groups (155 and 64

children, respectively). At 8–9 years of age, the children demonstrated delays in reading (35–41% as compared to 13–15% among peers) and arithmetic (20 to 39% as compared to 9–12% among peers). At both 5.5 and 9 years of age, the survivors of moderate encephalopathy were also found to perform significantly lower than the comparison cohort when everyday motor, complex motor and fine motor skills were assessed. Marlow and colleagues have evaluated another regional cohort of 65 children born 1992–1994 with neonatal encephalopathy at 7 years[3]. Disability was noted among 6% of children with moderate encephalopathy and 42% of those with severe encephalopathy; 15 children had disabling CP and 8 of the 15 had severe cognitive impairment (IQ <55). Among children without CP, IQ scores were similar between children with moderate encephalopathy and the comparison classroom peers, while those with severe encephalopathy scored 11.3 points lower on average with their peers. Attention and executive function and memory were impaired in the severe encephalopathy group and both encephalopathy groups had special education needs. In another study Odd et al compared children born 1991–92 and resuscitated at birth who developed encephalopathy (n=40) with children resuscitated at birth but asymptomatic for encephalopathy (n=612) and reference infants not resuscitated (n=8080), between 8 and 11 years of age[5]. Infants who developed encephalopathy had lower working memory (93.5 ± 11.9 vs. 100 ± 15, p=.065)), reading accuracy (92.1 ± 13.7 vs.100 ± 15), and language comprehension (90.9 ± 16.4 vs. 100 ± 15.8, both $p<0.05$) and increased need for educational support (14.3% vs. 2.9%, p=0.09) compared to the children who were well at birth. This association was no longer noted when children with CP were excluded.

Behavioral outcomes in children with a history of neonatal encephalopathy (between 1993–97) have been assessed among 34 children with mild encephalopathy, 47 with moderate encephalopathy and 53 normal control children[6]. Compared to control children, children with mild and moderate encephalopathy had more social problems and thought problems, and moderate encephalopathic children had higher anxious/depressed scores, attention problems and total problems. In another study, behavioral outcomes after moderate encephalopathy were assessed among 28 teenage 15–19 year olds, born in 1985 with siblings as controls[7]. Attention-deficit hyperactivity disorder, developmental coordination disorder, problems with memory, time perception and orientation were noted with higher frequency among the teenagers with moderate encephalopathy along with difficulties in making friends or interacting with peers.

An association between moderate or severe neonatal encephalopathy and autism has been reported in a population-based study of children born between 1993 and 96[8]. At age 5 a diagnosis of autism spectrum disorder was noted among 12 of 239 survivors of neonatal encephalopathy compared to 5 of 563 controls, OR 5.9, 95% confidence interval (CI) 2.0–16.9.

Prior to the era of hypothermia for neuroprotection, mortality rates were high among infants with severe HIE and children who survived neonatal encephalopathy had cognitive deficits even in the absence of functional deficits. Non-disabled children had fine-motor dysfunction and delayed entry into primary school and educational support needs were increased among both moderate and severe HIE children. It should be noted, however, that the majority of studies evaluating outcomes of term neonates with birth depression or encephalopathy have

generally been cohort studies, each study having unique inclusion criteria, evaluation methods and duration of follow-up.

Imaging studies prior to hypothermia therapy

Imaging studies have been examined as predictors of childhood outcome among cohorts of children with encephalopathy. The initial MRI scoring system evaluating correlation with neuromotor outcome was described by Barkovich[9]. Fifty-three infants with birth acidosis (pH <7.1, base deficit >10 and 5 min Apgar score <5) had neonatal MRI with known 3-month outcome, including 36 infants with 12 month outcome. A basal ganglia (BG) score, a watershed (W) score, the combined BG/W score and the sum of the BG and W score were described. The BG/W score correlated well with the 3- and 12-month motor and cognitive outcome. In a larger cohort, the pattern of injury and 30-month outcome was evaluated among 173 infants with neonatal encephalopathy[10]. The WS pattern of injury was seen in 78 (45%), BGT in 44 (25%) and normal MRI in 51 (30%) of infants. The BGT pattern was associated with the most impaired motor and cognitive outcome at 30 months. Investigators in the UK have also evaluated MRI patterns of injury: the scans were classified into 8 categories: a) normal, b) minimal BG and thalamus (T) only, c) moderate WM only, d) moderate BGT with equivocal posterior limb of the internal capsule (PLIC), e) moderate WM and BGT and PLIC, f) severe WM only, g) severe BGT and PLIC with focal WM and h) severe BGT, PLIC and diffuse WM involvement[11,12]. The scores were correlated with outcome to 4 years among 53 children. Children with minor MRI imaging findings did well neurologically while those with severe BG and WM lesions had restricted mobility or limited self-mobility at 2 and 4 years of age. Another report evaluated term infants with low one minute Apgar scores (n=68) and neurological abnormalities in the first 48 hours after birth and neonatal MRI who were followed to 5 to 6 years of age[4]. Fifteen (22%) died in the neonatal period; of the surviving infants 19 (36%) had cerebral palsy while the remaining 8 (15%) had minor neurological dysfunction and/or perceptual-motor difficulties, 1 (2%) had only cognitive impairment and 25 (57%) were normal. Eighty-three percent of children with a normal outcome had a normal neonatal MRI or minimal WM lesions, while 80% of those with minor neurological dysfunction and/or perceptual motor difficulties had mild or moderate BG or more marked WM lesions. The association of neonatal MRI and outcome among the non-disabled child (without functional motor deficits) has been assessed. Lower verbal IQ was noted with increasing degree of injury to the WS distribution among 81 children at 4 years of age[13]. Thus neonatal MRI predicted childhood outcome in cohorts of infants with perinatal asphyxia/encephalopathy[14].

Childhood outcomes following hypothermia for neonatal encephalopathy

Childhood Outcomes at 6–7 years in the NICHD Trial

The randomized controlled trials (RCTs) of hypothermia for neonatal encephalopathy had specific inclusion criteria and consistent follow-up; the earlier report of the NICHD Neonatal Research Network RCT of whole-body hypothermia for neonatal HIE noted the rate of death or moderate or severe disability at 18 to 22 months of age was 62% in the control group versus 44% in the hypothermia group (p=0.01), with a mortality rate of 37% and 24% respectively (p=0.08). There was no increase in the rate of severe disability in the

hypothermia group; the rates of moderate or severe CP were 30% in the control and 19% in the hypothermia group, with corresponding rates of blindness of 14% versus 7% and hearing impairment of 6% versus 4%[15]. The knowledge gap was whether the neuroprotective effects of hypothermia for neonatal HIE at 18 months of age persisted to childhood; therefore, the childhood outcomes study was designed to evaluate rates of death, cognitive impairment, and behavioral outcomes. The primary outcome at 6–7 years of age was death or IQ <70 while secondary outcomes included death, severe disability, components of disability, higher cognitive function, and psychosocial health[16]. Assessment tools included the evaluation of IQ with the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) (n=96) and the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (n=18). Verbal comprehension, perceptual organization and processing speed were assessed yielding a verbal IQ and performance IQ that are combined to give a full-scale IQ (normal value 100+15). Higher cognitive function was assessed by subtests of attention, executive function and visuospatial reasoning using the Developmental Neuropsychological Assessment (NEPSY, mean 100+15). Lastly, the Child Health Questionnaire assessed physical, emotional and social wellbeing of the child and the effects of the child's health on the parents. All testing was conducted by examiners trained to reliability and unaware of treatment assignment. The gross motor function of those with CP was evaluated using the Gross Motor Function Classification System (GMFCS) for 6–7 year old children: GMFCS level 1, walking without restriction; level II, walking without assisted device; level III, walking with an assistive device; level IV, self-mobility with limitation; and level V, severe limitation of mobility. *Severe disability* was defined as IQ >3 SD below the standardized test mean (<55), GMFCS level IV or V, or bilateral blindness. *Moderate disability* was IQ 2–3 SD below the mean (55–69), a GMFCS level of III, bilateral deafness (with or without amplification) or refractory epilepsy. *Mild disability* was IQ 1–2 SD below the mean (70–84) and a GMFCS level I or II. *No disability* was defined as IQ less than 1 SD below mean (>84) with no CP, hearing or vision deficit or epilepsy. Among non-disabled survivors, *every day motor function* was tested by the heel-to-toe, ability to hop, stand on one foot or Romberg's test, while *fine motor function tests of coordination* included finger-nose, rapid alteration of hands, thumb index finger apposition, thumb– 4 finger apposition sequentially, heel to shin test and foot tapping. The primary outcome was adjusted for center and level of HIE at random assignment to cooling or control group.

Primary outcome data was available in 190 of 208 (91% of participants), 97 of 100 (97%) in hypothermia and 93 of 106 (88%) control group; 5 hypothermia (2 moderate and 2 severe HIE, 1 with seizures) and 13 control group children (12 moderate and 1 severe HIE) were lost to follow-up. The baseline characteristics of children with and without primary outcome data were similar except that mothers of children with primary outcome were more likely to be white and married and children more likely to have lower cord pH. The baseline characteristics of children in the 6–7 year analysis were similar except that mothers of children in the hypothermia group had higher frequency of antepartum hemorrhage. The primary outcome was seen in 46/97 (47%) hypothermia and 58 of 93 (62%) control group; adjusted relative risk (RR) 0.78 (0.61–1.01). The mortality rate was 27 of 97 (28%) hypothermia vs. 41 of 93 (44%) control, adjusted RR 0.66 (0.45–0.97); 3 in each group died after the 18–22 month visit. Death or severe disability was 41% vs. 60% (p=0.03), death or

IQ < 55 was 41% vs. 60% (p=0.03) and death or CP was 41 vs. 60%, (p = 0.02 in the hypothermia and control groups, respectively). Among survivors IQ <70 occurred in 27% vs. 33%, CP 17% vs. 29% (both p=NS). Attention and executive function <70 occurred among 2/48 and 4/32 children and visuospatial scores <70 among 2/53 and 1/36 children who could be tested in the hypothermia and control group (p=NS). There were no differences between groups when parental assessment of child's self-esteem was evaluated; the emotional impact of the child's wellbeing on parents was also similar between groups. There were no differences between groups in the parental assessment of the child's physical health.

The NICHD trial reported detailed cognitive outcomes in a secondary study of all children followed at 18 to 22 months and at school age[17]. 30 children were lost to follow-up (12 in the hypothermia group and 18 in the normothermia group). 19 children were deemed so severely impaired as to preclude psychometric evaluation and were assigned a Full Scale Intelligence Quotient (FSIQ) of 39; functional outcomes in these children were assessed with the Pediatric Evaluation of Disability Inventory. No scores were imputed for verbal IQ, performance IQ or processing speed. FSIQ scores were <85 in 52% of the participants randomized to hypothermia and <70 in 25% compared to <85 in 53% of normothermia and <70 in 32% of hypothermia participants. Mean FSIQ scores were 80.9 + 23.3 and 75.3 + 24.4 respectively among the hypothermia and normothermia groups. Mean verbal IQ and performance IQ scores were similar between the two groups (verbal IQ score was 85.9 and 86.4 among the hypothermia and normothermia groups; performance IQ score was 91.3 and 90.5 respectively). Overall, 96% of survivors with CP had an IQ <70; 9% of children without CP had a FSIQ <70, and 31% had a FSIQ of 70 to 84. Among children with an IQ<70, 23% had normal gait, 6–16% had the ability to perform complex motor functions and 10% had intact fine motor function. Twenty percent of children with normal IQ and 28% of those with IQ 70–84 received special educational support services or were held back ≥1 grade level. Thirty two percent of children in the hypothermia group who were functioning at a level that permitted formal IQ or neurodevelopmental testing required special educational services.

Clinical predictors of outcome at 6–7 years in the NICHD Trial—Among children in the trial who had moderate or severe disability at 18 months, the corresponding rates at 6–7 years was 15 of 17 (88%) in the hypothermia and 18/19 (95%) in the control group[16]. All children with CP at 18 months had CP at 6–7 years; among those with seizures at 18 months the corresponding rate at 6–7 years were 4/10 (40%) hypothermia and 5/10 (50%) control group, respectively. The predictive value of moderate or severe disability at 6–7 years for children disabled at 18 months in the hypothermia group was sensitivity 63%, specificity 96%, positive predictive value (PPV) 88% and negative predictive value (NPV) 83% while the corresponding rates in the control group were 95%, 97%, 95% and 97%, respectively. The predictive value of moderate or severe CP at 6–7 years for children with moderate or severe CP at 18 months had a sensitivity 100%, specificity 100%, PPV 100% and NPV 100% in the hypothermia group and 93%, 100%, 100%, and 97% in the control group respectively. The odds of disability at 6–7 years for an infant disabled at an earlier age, compared to one not disabled was 37 times higher (95% CI 7–189) in the hypothermia group

and 576 times higher in the control group (34-9774)[16]. Children with an 18–22 month Bayley-II mental development index (MDI) <70, had, on average an adjusted IQ at 6 to 7 years of age that was 42 points lower than that of those with an MDI >84[17]. Thus, a high concordance was noted between assessment of moderate or severe disability at 18–22 months and similar assessments to 6–7 years of age. The major conclusion from the NICHD study is that the neuroprotection of hypothermia for HIE noted at 18 months continues to childhood. The significant reduction in death was not accompanied by an increase in survivors with disability; the survival rate of children at 6–7 years with moderate or severe HIE in the hypothermia group was 72% compared to 56% in the control group while moderate or severe disability was 35 and 38% respectively. There was a high concordance for assessment of moderate or severe disability between the 18 months and 6 to 7 years of age.

10-minute Apgar score and childhood outcomes in NICHD trial—Natarajan and colleagues determined the association between 10 min Apgar scores and 6–7-year outcomes in children enrolled in the NICHD NRN whole body cooling trial[18]. Rates of adverse outcomes were generally higher with lower 10 min Apgar scores and lower in cooled (n=90) infants compared with controls (n=84), especially at lower Apgar scores, although the numbers were small. Mortality rate of cooled infants was 26/90 (28.9%) compared with 39/84 (46.4%) for those receiving standard care. After adjustment for center, birth weight, gestational age, gender, treatment group and outborn status, each point increase in the 10 min Apgar scores was associated with a significantly lower risk of death/disability [OR 0.68; 95% C.I. 0.57–0.82)], death/IQ <70 [OR 0.68; 95% C.I. 0.57–0.82)], death [OR 0.69; 95% C.I. 0.58–0.83)], death/CP [OR 0.64; 95% C.I. 0.52–0.77)] and among survivors, moderate/severe disability, IQ <70 and CP. The risk-adjusted probabilities were significantly lower in cooled infants; there was no interaction between cooling and Apgar scores. Among the 24 children with a 10 min Apgar score of 0, there were 11 survivors of whom five (20.8%) survived without moderate/severe disability (3 of the children underwent cooling). Their median IQ was 90 (range 77–99); three had moderate and two had severe HIE at randomization at <6 hours of age. Their median (range) scores for attention/executive function were 92 (72–110) and their median (range) scores for visuospatial function were 90 (82–132). Two of the infants had mild disability (IQs 77 and 83) while the remaining three had no disability. Five other survivors with 10 min Apgar scores of 0 had moderate/severe disability at both 18 months and 6–7 years of age and one had missing CP data. These data among trial infants lend support to the 2011 International Liaison Committee on Resuscitation and Neonatal Resuscitation Program recommendations that the decision to continue resuscitation may be influenced by the etiology of the arrest, gestational age, time of initiation of resuscitation, the potential role of therapeutic hypothermia and parental views.

Temperature profiles and childhood outcomes in NICHD Trial—A subset (n=89) of the NICHD NRN randomized trial cohort in whom temperature profile and follow-up data at 6–7 years were available was used to determine if higher temperature in the initial few days of life affected early school age outcome among infants with encephalopathy cared for without hypothermia[19]. Infants with at least one esophageal temperature ≥ 38°C (n = 44) in

the first few days of life differed from infants with all esophageal temperatures < 38°C (n = 45) in birth weight (3558 ± 556 vs 3133 ± 545 grams, p=.0005) but were similar in gestational age, gender, delivery room intubation, Apgar at 10 minutes, cord pH and base deficit, and level of encephalopathy. At 6 to 7 years, death (n=37) or IQ<70 (n=17) occurred in 54 children while 35 children had an IQ ≥ 70. There were 15 infants with CP including 9 spastic quadriplegic, 2 dystonic, 1 choreo-athetotic, 1 ataxic and 2 undesignated CP. Death or IQ<70 was associated with the upper quartile average of esophageal (OR 7.3, 95% CI=2.0–26.3) and skin temperature, (OR 3.5, 95% CI=1.2–10.4). CP was associated with the upper quartile average of esophageal (OR 12.5, 95% CI=1.02–155) and skin temperature (OR 10.3, 95% CI=1.3–80.2). The average of the highest quartile for esophageal temperature, the median esophageal temperature and the highest quartile of skin temperature were all associated with increased odds of death alone. There were no associations between temperature and an IQ <70 alone. Whether elevated temperature in HIE is a marker of brain injury or exacerbates the injury could not be determined.

Relationship of Childhood Outcomes and the Parental Perception of Functional status and Impact on the Family in NICHD Trial—Parents of infants who participated in the NICHD NRN whole body cooling randomized controlled trial completed three questionnaires at the 18–22 month follow-up visit to address a) the functional status (FS) of their children (FS-II questionnaire) b) resources available (Family Resource Scale-FRS) and c) the impact on the family (IOF questionnaire) of having a child with HIE[15]. These parental assessments were compared in groups of surviving children who were diagnosed with no/mild disability (n=74) and those with moderate/severe disability (n=37) at 6–7 years of age[20]. The association between functional status at 18 months of age and disability at 6–7 years of age was examined, while controlling for neonatal and family variables and impact on the family. Severe HIE (32 vs. 15%) and public insurance (73 vs. 47%) were significantly more frequent in children who had disability, compared to survivors with no or mild disability at 6–7 years of age. Mean (SD) FS-II general health and independence scores, total FRS scales, and the FRS subscale for money were significantly lower in this group. The IOFS reflected a greater total impact, financial impact, and caregiver and family burden, and greater disruption of planning in those who had moderate or severe disability, although coping was similar in both groups. In the regression model, each unit increase in the FS-II independence score was associated with a reduction in moderate or severe disability (OR 0.92; 95% CI 0.87–0.97). The area under the curves was 0.935 when FS-II and IOFS data were included. The path analysis revealed that children with severe HIE and those whose families reported greater impact had significantly poorer FS-II independence and general health scores at 18 months of age. Public insurance was associated with poorer FS-II independence scores. FS-II general health and independence scores at 18 months of age were strongly correlated; independence, but not general health, at 18 months of age was associated with disability at 6 to 7 years of age. This study revealed a novel interaction between disease-related factors, family socioeconomic status and impact, parental perception of functional impairment, and eventual childhood outcomes in the context of neonatal HIE. The authors suggest that disease-related outcomes of children may be affected by the stressful impact on families and may potentially be improved with family-level support.

Cerebral Palsy and growth in Childhood survivors of HIE in NICHD Trial— Through a secondary analyses of follow-up data at 18 months and 6–7 years of age among the surviving NICHD NRN whole body cooling trial participants, Vohr and colleagues compared longitudinal weight, head circumference, and length measurements from birth to 6 to 7 years of age for children with moderate or severe CP (n=23) and those without CP (n=92) Vohr[21]. Children with CP were more likely to have had severe HIE, require post discharge oxygen, gavage feeding, or gastrostomy feeding and receive anticonvulsant medication ($P = .001$). At 18 to 22 months, 14% of children with moderate or severe CP were reported to independently feed themselves compared with 95% without CP; $P < .0001$ and 59% had re-hospitalizations compared with 25% of those without CP ($P = .004$). Children with CP had high rates of severe motor (96% vs. 7%) and cognitive impairment (96% vs. 8%) with 87% having a Bayley II MDI and Psychomotor Developmental Index (PDI) <50. At 6–7 years of age, 52% of the CP group received gastrostomy feeds and 87% and 83% respectively were receiving physical and occupational therapy, compared to 0%, 7% and 9% for the group without CP. The re-hospitalization rate continued to be higher (18 [78%] vs 23 [25%]; $P < .0001$) at 6–7 years of age. A greater proportion of children with CP had weights (59% vs. 2%), lengths (47% vs. 15%) and head circumferences (73% vs. 7%) <10th centile at 18–22 month follow-up. Rates of head circumference <10th percentile increased for children with moderate or severe CP from 73% to 82% between 18–22 months and 6–7 years. The proportion of extreme severity of weight restriction at 18–22 months and 6–7 years (WT z score ≤3) for children with CP (14%, and 24%) were significantly higher than in the No CP group (0%, and 0%), respectively ($P = .007, .0001$). In time-oriented logistic regression models, moderate to severe CP was the strongest predictor of weight, height and head circumference below the 10th percentile. Re-hospitalizations at 6 to 7 years was significantly associated with an HC <10th percentile (OR = 4.99; CI = 1.23–20.20; $P = .03$). Children with CP developed worsening growth failure with increasing age, whereas those without CP had evidence of catch-up growth. Among those with CP alone, gastrostomy was beneficial for weight z score (adjusted mean difference in z score = 1.02; $P = .006$), and the hypothermia treatment group was beneficial for length z score (adjusted mean difference in z score = 0.63; $P = .01$). The burden of health and neurocognitive problems in children with CP suggests the need for close monitoring and early intervention.

Childhood Outcomes at 7–8 years in the CoolCap Trial

The CoolCap study goal was to evaluate whether 18–22 month neurodevelopmental outcomes predicted functional outcomes at 7–8 years of age among surviving children[22]. The authors reported on WeeFIM ratings in childhood on 62 of 135 surviving children assessed at 18 months; 32 in the cooled group and 30 in the control group. Self-care, mobility and cognitive function were assessed qualitatively through parent interview by a single individual over the phone. There was 1 refusal, 58 lost to follow-up and 14 children whose centers declined to participate. The baseline characteristics and 18 month primary outcome data of the children with WeeFIM ratings at 6–7 years was not different from those of the children not assessed. There were no differences in the baseline characteristics of the study cohorts except for trend for more of the cooled subjects to have severe HIE compared to controls. Disability status at 18 months was strongly associated with WeeFIM ratings ($p<0.001$); there was no significant effect of treatment. A favorable outcome at 18 months

predicted WeeFIM ratings with a sensitivity of 87%, specificity of 56%, and PPV of 74% and NPV of 74%. Thus the authors note that functional outcome at 7–8 years is associated with 18 month neurodevelopmental assessment.

Childhood Outcomes at 6–7 years in the TOBY Trial

The Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial evaluated neurocognitive function of trial participants at 6–7 years of age with a primary outcome of survival with IQ ≥85[23]. The IQ was assessed by the WPPSI III or the WISC IV and attention and executive function, visuospatial processing, sensorimotor function and memory and learning was assessed by the NEPSY. In addition, central executive function, and verbal and non-verbal short-term memory was evaluated by the Working Memory Battery test for Children. The neurological examination included the GMFCS assessment. Parental and teachers completed the Strengths and Difficulties Questionnaire and the Attention Deficit–Hyperactivity Disorder (ADHD) rating Scale IV. Parents were also asked to complete questionnaires regarding child behavior and utilization of health care services.

Outcome data were available for 280 of 325 enrolled in the RCT (184 survivors and 96 who died), 18 hypothermia group and 25 control group children were lost to follow-up and an additional 41 children were unable to complete IQ testing (37 with severe physical impairment and 4 who would not cooperate). No scores were imputed for the severely disabled children, although they were all deemed as having subnormal IQ. As compared with participants, nonparticipants had a higher rectal temperature at randomization, were less likely to enter study at <4 hours, and had a higher frequency of aEEG abnormalities at study entry and lower Bayley II MDI scores at 18 months. The primary outcome of survival with an IQ ≥85 occurred among 75 of 145 children (52%) in the hypothermia group vs. 52 of 132 (39%) in the control group, (RR 1.31, 95% CI 1.01–1.71). The mortality rate was 47/162 (29%) and 49/162 (30%) in the hypothermia and control groups, respectively. More children in the hypothermia group than the control group survived without neurological abnormalities and with better motor-function scores, while rates of CP, and moderate or severe disability were lower compared to the control group (all $p<0.05$). There were no significant differences between groups in the parental assessments of health status and in psychometric tests except that attention-executive scores were higher among children who could be tested among the hypothermia group compared to control children. Use of special education resources was also lower in the hypothermia group compared to control group children. The study conclusion is that moderate hypothermia after perinatal asphyxia resulted in improved neurocognitive outcomes in middle childhood.

Imaging Predictors of Outcome following hypothermia for neonatal HIE—Three of the hypothermia for neonatal HIE RCTs have reported on the neonatal MRI as a biomarker of outcome at 18–24 months of age in subsets of trial participants. The neonatal MRI results of the TOBY trial demonstrated a reduction in lesions in the BGT, WM and the PLIC among cooled infants (n=64) compared to control infants (n=67) with a predictive ability of death or disability at 18 months of age of 84% in the cooled group and 81% in the control group[24]. The Infant Cooling Evaluation (ICE) trial group noted WM injury was decreased on the neonatal MRI among cooled infants (n=66) compared to the non-cooled

group (n=61) and PLIC and BGT injury were associated with death or disability at 24 months of age[25]. The NICHD NRN trial group described a decrease in areas of infarction in the watershed (WS) area among infants in the hypothermia group (n=73) compared to the control group (n=63) and described an MRI pattern of injury.[26] In this scoring system, each level reflects a greater involvement of brain injury: 0, normal; 1A, minimal cerebral lesions only with no involvement of BG or thalamus (T) or anterior limb of the internal capsule (ALIC) or posterior limb of the internal capsule (PLIC) and no area of watershed infarction; 1B, more extensive cerebral lesions without basal ganglia and thalamic (BGT), PLIC or ALIC involvement or infarction; 2A, any BGT, ALIC or PLIC involvement or watershed infarction noted without any other cerebral lesions; 2B, involvement of either BGT, ALIC or PLIC or area of infarction and additional cerebral lesions; and 3, cerebral hemispheric devastation. The brain injury pattern correlated with outcome of death or disability and with disability among survivors. Each point increase in the severity of the pattern of brain injury was independently associated with a twofold increase in the odds of death or disability. The NICHD scoring pattern is biomarker for death or moderate or severe disability at 18–22 months in the setting of neonatal encephalopathy.

The relationship between the neonatal MRI and childhood outcome was examined in the NICHD NRN trial among 124 children of 208 trial participants who had both neonatal MRI and data on the primary outcome of death or IQ <70 at 6–7 years of age[27]. Death or IQ <70 occurred in 4 of 50 (8%) with pattern 0, 1 of 6 (17%) with pattern 1A, 1 of 4 (25%) with 1B, 3 of 8 (38%) with 2A, 32 of 49 (65%) with 2B and 7 of 7 (100%) with pattern 3, p<.001. The relationship of pattern of injury and outcome at 6–7 years was also seen within the hypothermia and control groups. IQ was 90±13 among the 46 children with normal neonatal MRI and 69±25 among the 50 children with an abnormal MRI. For a normal outcome at 6–7 years of age, a normal neonatal MRI had a sensitivity of 61%, specificity of 92%, and PPV of 92% and a NPV of 59%. For death or IQ <70, the 2B and 3 pattern combined had a sensitivity of 81%, specificity of 78%, PPV of 70% and NPV of 87%. Thus the NICHD NRN MRI pattern of neonatal brain injury is a biomarker of neurodevelopmental outcome at 6–7 years of age.

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