HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

J Pediatr. 2017 August ; 187: 26–33.e1. doi:10.1016/j.jpeds.2017.03.065.

The frequency and severity of MRI abnormalities in infants with mild neonatal encephalopathy

BH Walsh[1,2], **J Neil**[3], **J Morey**[1], **E Yang**[4], **V. M Silvera**[4], **TE Inder**[1], and **C Ortinau**[1]

[1]Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Boston, USA

[2]Division of Newborn Medicine, Boston Children's Hospital, Boston, USA

[3]Department of Neurology, Boston Children's Hospital, Boston, USA

[4]Department of Radiology, Boston Children's Hospital, Boston, USA

Abstract

Objective—To assess and contrast the incidence and severity of abnormalities on cerebral magnetic resonance imaging (MRI) between infants with mild, moderate, and severe neonatal encephalopathy who received therapeutic hypothermia.

Study design—This is a retrospective cohort study of infants with mild, moderate, and severe NE who received TH at a single tertiary neonatal intensive care unit (NICU) between 2013 and 2015. Two neuro-radiologists masked to the clinical condition evaluated brain MRIs for cerebral injury following TH using the Barkovich classification system. Additional abnormalities not included in this classification system were also noted. The rate, pattern, and severity of abnormalities/injury were compared across the grades of NE.

Results—Eighty-nine infants received TH and met study criteria – 48 with mild NE, 35 with moderate NE, and six with severe NE. Forty-eight infants (54%) had an abnormality on MRI. There was no difference in the rate of overall MRI abnormalities by grade of NE (mild NE 54%, moderate NE 54%, and severe NE 50%, p=0.89). Basal ganglia/thalamic injury was more common in those with severe NE (mild NE 4%; moderate NE 9%; severe NE 34%, p=0.03). In contrast, watershed injury did not differ between NE grades (mild NE 36%; moderate NE 32%; severe NE 50%, p=0.3)

Conclusion—Mild NE is commonly associated with MRI abnormalities after TH. The grade of NE during the first hours of life may not adequately discriminate between infants with and without cerebral injury noted by MRI after TH.

The authors declare no conflicts of interest.

Figure 1; online: MRI images of an infant with mild NE- On day 4 of life, DWI changes consistent with insult to the left anterior and posterior watershed regions, and left thalamus. By day 10, the DWI is pseudonormalized, but T2 images indicate injury in affected regions

Keywords

Mild encephalopathy; Neonatal Encephalopathy; Hypoxic-Ischemic Encephalopathy; Asphyxia; Magnetic Resonance Imaging; Therapeutic Hypothermia

Infants with moderate to severe neonatal encephalopathy (NE) are at risk for adverse neurodevelopmental outcomes, including cerebral palsy, cognitive delay, and neuro-sensory impairments.[1] Randomized, controlled trials (RCT) of therapeutic hypothermia (TH) in term-born infants with moderate and severe NE have demonstrated a 25% reduction in the risk of death or disability.[2–4] Thus, TH has become a routine practice across neonatal intensive care units (NICUs). Although TH improves outcomes for moderate and severe NE, whether this therapeutic benefit applies also to infants with mild NE is unclear.

Mild NE has previously been considered a benign clinical syndrome with a good long-term prognosis.[1, 5] For this reason, and due to concerns about the potential side effects of TH, infants with mild NE were not eligible for the previous RCTs. However, there has been an increasing trend to provide TH to newborns with mild NE.[6–8] There are several potential explanations for this. First, the clinical examination evolves over time following brain injury,[9, 10] such that a single exam within the first 6 hours of life may not reflect the full extent of injury.[1, 10] Second, although the morbidity associated with mild NE has been thought to be low,[1, 5] recent observational studies have demonstrated greater morbidity than previously recognized, including both short-term[7, 11] and long-term complications.[12–14] However, data are lacking in this population to document systematically the incidence and patterns of cerebral abnormalities in infants with mild NE who underwent TH. Therefore, this study aimed to describe the MRI findings in infants with mild NE following TH and to compare the severity of cerebral injury defined on MRI with that of infants with moderate or severe NE following TH.

Methods

This retrospective cohort study included all infants who underwent TH between September 2013 and December 2015 in a single tertiary level NICU. Institutional Review Board approval was obtained. The inclusion criteria for TH in our center are modified regional center based criteria in which variables have been broadened from those used in the RCTs.[3, 15] These criteria were developed due to concerns regarding the poor specificity of some of the RCT variables for NE,[16–18] along with recognition of greater morbidity in mild NE.[11, 19]The adaptations have included: (1) decreasing the gestational age criteria to >34 weeks; (2) increasing the inclusion pH from ≤ 7.0 to ≤ 7.1; (3) reducing the base excess for inclusion from ≥−16 mEq/L to ≥−12 mEq/L; and (4) providing TH to infants with mild NE on clinical examination, in addition to those with moderate or severe NE (Table I). All infants in this study were born after the change in the local criteria. The inclusion criteria required that TH be initiated within the first 6 hours of life, in keeping with the RCTs. Infants with confounding conditions that may have independently resulted in abnormalities on the cerebral MRI were excluded from this analysis.

The clinical grade of encephalopathy was assigned following combined assessment by both a child neurologist and neonatologist. The grade of NE was defined as either mild, moderate, or severe, based upon a well validated standardized neurological exam.[4, 10] The initial neurological assessment performed in the first hours of life prior to initiation of hypothermia is utilized here when defining severity of encephalopathy.

Following clinical assessment and encephalopathy grading, aEEG monitoring was initiated, typically within the first hours of life. This was performed using either an Olympic Cerebral Function Monitor (CFM) 6000 or an Olympic Brainz (Natus, San Antonio, CA), and was prospectively graded using the amplitude classification system described by al Naqeeb et al.[20] The aEEG monitoring was transitioned to continuous multi-channel video-EEG (cEEG) after initiation of TH and remained in place for the duration of hypothermia and rewarming. The cEEG recordings were reviewed for the presence and timing of electrical seizures. This information was not a part of the clinical assessment of severity of NE. However, the data were used in this cohort for secondary analysis to assess 1) whether re-classifying mild infants with seizure activity into the moderate NE category influenced the primary results and 2) whether incorporation of background pattern on aEEG or presence of seizures was able to differentiate significant MRI abnormalities.

Demographic, clinical, and laboratory data, including maternal prenatal history, delivery history, and postnatal history until discharge were collected. These included data on potential side effects of TH that were identified from the literature,[221] such as the presence of significant arrhythmias, leukopenia (white blood cell count $< 5 \times 10^9$/L), thrombocytopenia ($<150 \times 10^9$/L), major hemorrhage (defined as bleeding necessitating immediate transfusion of blood product), blood product use, subcutaneous fat necrosis, and persistent pulmonary hypertension (PPHN).

Magnetic Resonance Imaging

All infants underwent at least one cerebral MRI performed after TH within the first week of life. The clinical team caring for the infant determined whether a second MRI was required. There was significant variation in acquisition of a second MRI, which appeared to be influenced by the results of the first MRI (75% of infants with an abnormality on the first MRI, compared with 44% of infants with a normal first MRI, underwent a second MRI). Because of this variability and the potential for selection bias in the results of the second MRI, only data from the first MRI were used for our primary analysis. However, additional analysis was performed on the second MRI data to evaluate for differences in cerebral injury on the second MRI across all grades of NE.

All scans were performed on a 3-T Siemens scanner (Siemens, Erlangen, Germany). The standard clinical imaging protocol included sagittal motion corrected magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted (T1) images (repetition time [TR] of 2800 msec, echo times [TE] of 2.75, 4.68, 6.54 and 8.4 msec, flip angle 7°, voxel size of 1 × 1 × 1 mm), axial turbo spin echo [TSE] T1 images (TR of 574 msec, TE of 13 msec, flip angle 140°, voxel size of 0.5 × 0.5 × 3 mm, echo train length of 2), axial TSE T2-weighted (T2) images (TR of 9000 msec, TE of 150 msec, flip angle 120°, voxel size of 0.5 × 0.5 × 3 mm, echo train length of 19), and coronal TSE T2 images (TR of 9210 msec, TE of 187

msec, flip angle 130°, voxel size of 0.4 × 0.4 × 3 mm, echo train length of 19). Diffusion weighted imaging (DWI) using multidirectional diffusion weighted measurements (TR of 6200 msec, TE of 92 msec, 1984 Hz/Px bandwidth, 140 mm field of view, 2 × 2 × 2 mm voxels, 30 b-directions with amplitudes ranging from 0 to 1000 s/mm^2).

The images for this study were analyzed by a pediatric neuroradiologist (E.Y.) blinded to the clinical grade of encephalopathy. The presence and type of any MRI abnormalities were compiled. Detailed analysis of the pattern of brain injury was then performed, classifying the findings according to the grading system developed by Barkovich et al,[22] which has been validated in neonatal encephalopathy using both conventional and diffusion weighted sequences.[23] A score of ≥2 in the deep nuclear grey matter, or a score of ≥3 in a watershed pattern, was considered consistent with moderate-severe MRI injury (Table II).[24, 25] To ensure validity of these results, a randomly chosen subset of 30 MRI scans was reviewed by a second independent neuroradiologist (VMS). For MRIs assigned discordant grades, consensus was reached in a joint reading.

Statistical Analyses

Statistical analysis was performed using PASW statistics 18.0. Non-parametric data were reported as median values with inter-quartile range (IQR) or range as specified in the text, and comparisons performed using the Mann-Whitney U test or Kruskal-Wallis H Test, as appropriate. The chi squared test was used when comparing proportions. Agreement between the MRI reviewers was assessed using kappa scores, and the percentage of scans that was agreed upon was additionally reported. Statistical significance was taken as $p<0.05$, and a Bonferroni correction was applied for post hoc subgroup analysis.

Results

Between 2013 and 2015, 136 infants were evaluated for TH and 95 were treated with TH. Of the 41 infants evaluated but not treated, 40 were born at ≥36 weeks gestation and one infant was born at 35 weeks gestation. One infant who was evaluated but not treated had mild NE (GA ≥ 36 weeks). Ninety-five infants were treated with TH, six of whom were excluded from the analysis, including three who had a genetic/metabolic syndrome and three who received ECMO. The three infants treated with ECMO had documented PPHN prior to initiation of TH. This left a study sample of 89 infants, 48 with mild NE, 35 moderate NE, and six with severe NE. Demographic, perinatal, and short-term clinical outcomes data are all displayed in Table III. Of note, despite the inclusion criteria of a gestational age >34 weeks, there were only five infants treated who were born at <36 weeks, all of whom were 35 weeks gestation at birth (one infant with mild NE, three with moderate NE, and one with severe NE).

MRI Outcome

All 89 infants had an MRI scan within the first week of life, and 53 (59%) had a subsequent second scan (29 with mild NE, 21 with moderate NE, and 3 with severe NE). There was no difference between encephalopathy groups for median day of life or postmenstrual age at the time of the first or second MRI (Table III). Reliability testing for MRI scoring revealed good

agreement between MRI raters for both the presence of any MRI abnormality (89% agreement; kappa score 0.76, p<0.001) and the presence of moderate-severe MR injury on the Barkovich score (93% agreement; kappa score 0.71, p<0.001). Forty-eight infants (54%) had an abnormality on their first MRI scan. No difference could be detected between grades of NE for the rate of abnormalities occurring. Twenty-six (54%) infants with mild NE, nineteen (54%) infants with moderate NE, and three (50%) infants with severe NE had an abnormal early MRI scan (p= 0.89). The most common finding was signal abnormality consistent with hypoxic-ischemic injury classifiable by the Barkovich system (Table IV and Figure; Figure available at www.jpeds.com). Of the injuries consistent with the Barkovich criteria, 92% (31/34) demonstrated restricted diffusion, in addition to the changes on conventional T1- and T2-weighted sequences, consistent with a recent hypoxic ischemic injury. The three cases that did not demonstrate abnormal restriction included one infant with mild NE, one with moderate NE, and one with severe NE.

The only difference identified between groups on the first MRI was the proportion of infants with basal ganglia/thalamic injury (p= 0.03), with a higher proportion of infants with severe NE demonstrating injury to the deep grey nuclei. However, this difference was not significant on *post hoc* analysis (significance taken as p<0.016 with Bonferroni correction: mild *vs*. moderate NE, p=0.08, mild *vs*. severe NE, p=0.02, moderate *vs*. severe NE p=0.15), likely as a result of the small number of infants with severe NE in this cohort. Nineteen infants (21%) had a moderate-severe MRI abnormality using the dichotomous MRI outcome as defined in Methods. There was no difference in the rates of moderate-severe MRI abnormality between grades of encephalopathy (p=0.62)(Table IV). For the second MRI, there was no difference between grades of NE for the rate of MR abnormalities (mild NE 62% [18/29], moderate NE 52% [11/2]), and severe NE 100% [3/3], p=0.28), rate of abnormalities classifiable by the Barkovich score (mild NE 44% [13/29], moderate NE 33% [7/21], and severe NE 67% [2/3], p=0.47), and rate of moderate-severe MRI abnormality (mild NE 28% [8/29], moderate NE 19% [4/21], and severe NE 33% [1/3], p=0.74).

Discussion

This retrospective observational study identifies that just over half of infants with NE (mild, moderate, or severe) and treated with TH had an abnormal MRI. More importantly, the study could not demonstrate a difference in the incidence of moderate-severe cerebral injury between all grades of NE. These findings are of greatest relevance to infants with mild NE, among whom 54% had an abnormality on cerebral MRI and 23% of them had moderate-severe cerebral injury. Finally, it is noteworthy that almost all infants with moderate-severe MRI cerebral injury had changes on diffusion weighted sequences, highlighting the perinatal timing of these injuries.

Although early studies suggested that severe neurological injury is infrequent in infants with mild NE,[5] our findings are consistent with recent studies that have found evidence of injury among these infants.[7, 11–13, 19] DuPont et al found that 20% (12/60) of infants with mild NE had an abnormal short-term outcome, including presence of seizures, abnormal neurological examination at discharge, and feeding difficulties beyond the first week of life. Few infants had MRIs in their cohort, nine in total, 66% of which were abnormal.[11] The Children's

Hospital Neonatal Database reported that 59% (89/132) of infants with mild NE from their network had an abnormality on MRI.[7] Additionally in a recent cohort study, Gange-Loranger et al reported that among 13 infants with mild NE who underwent TH, 31% (4/13) had MRI changes consistent with HI injury.[26] The rate of both any MRI abnormality, and MRI hypoxic-ischemic injury, among those with mild NE in these studies is consistent with our own findings. However none of these studies provided sufficient details regarding the pattern or severity of MRI cerebral injuries to allow further meaningful comparison across studies.

In addition to short-term neurological outcomes, recent data from infants with mild NE have documented long-term neuro-developmental morbidities in early childhood and at school age. Several recent studies in Europe, Australia, and China, have included details on developmental outcomes from infants with mild NE. This was not the primary aim of these studies, and therefore the sample sizes were relatively small (combined population of mild NE from the three studies was 103) and underpowered for neurodevelopmental assessment. Despite this, each of the studies reported neurodevelopmental deficits at 18 to 24 months of age among those children.

The rates of abnormal outcome following mild NE ranged from 10–30% depending on the study.[19, 27, 28] Similarly, later follow-up of infants with mild NE at school age has demonstrated that 50% of these children have abnormalities on MRI at nine to ten years of age.[29] Further, they have lower IQ scores and increased thought problems compared with healthy controls.[12]Although our data exclusively focused on neonatal MRI outcomes, these results support our findings of increased neurological risk in mild NE.

Based upon the known mechanisms of cellular injury and death following hypoxia ischemia,[9, 30] and our understanding of the neuroprotective mechanisms associated with TH,[9] there is biological plausibility for the use of TH among infants with milder encephalopathy. However, the original TH RCTs did not include infants with mild NE. The rationale for this was based on: 1) the adverse effects of TH were not yet known and it was difficult to justify treating mildly affected infants without knowledge of risk-benefit and 2) the effect size was likely to be greater in more severely affected infants, thereby assisting in a definitive outcome for the RCTs. Although none of the RCTs focused on the efficacy of TH in infants with mild NE, a small number of mildly encephalopathic infants were enrolled in two trials (total n=79).[19, 28] This may reflect the difficulty of firmly assigning the severity of NE within the first hours of life and is consistent with what often occurs in the clinical setting.[6–8, 31] Zhou et al randomized 39 infants with mild NE, 21 to treatment with TH and 18 controls.[28] Thirty-three percent (13/39) of those with mild NE were found to have a moderately abnormal outcome (a developmental quotient between one to two standard deviations below the mean at 18 months of age, using the Gesell Child Development Age Scale). Stratifying by treatment group, 29% (6/21) who received TH *vs.* 39% (7/18) of control infants had a moderately abnormal outcome (p=0.5). In the ICE trial, Jacobs et al randomized 40 infants with mild NE, 16 to treatment with TH and 24 controls.[19] Thirty percent (12/40) of infants with mild NE met the composite primary outcome of death or severe disability at two years of age. Stratifying by treatment group, 25% (4/16) who received TH *vs.* 33% (8/24) of control infants met the primary outcome (p=0.7). Although

these trials did not detect a significant difference in outcome among those with mild NE, it is important to recognize that they were neither designed nor powered to do so.

An important consideration when choosing to provide TH to infants with mild NE is the risk of TH administration. The literature to date has reported a relatively benign side effect profile, with increased risks for sinus bradycardia, thrombocytopenia, leukopenia, and subcutaneous fat necrosis reported to be associated with TH.[2, 6, 31] These data however, are based exclusively upon infants with moderate and severe NE and do not include those with mild NE. In our cohort, there were no significant cardiac arrhythmias and minimal leukopenia. We found the incidence of thrombocytopenia to be equal to that in higher grades of encephalopathy. However, only two infants with mild NE received a platelet transfusion and no infant with mild NE had a major hemorrhage. Eighteen percent of infants with mild NE did receive a blood product during their hospital course, with FFP being the most common product administered. Although our cohort demonstrated no significant adverse effects attributed to TH, further monitoring and study of the safety profile associated with its use in animal and human populations must continue[32] to ensure appropriate and safe therapy is provided.

Although our study has provided new information regarding the nature and pattern of MRI abnormalities in infants with mild NE, our does have several limitations. Our study lacked a control sample. Secondly, our sample size was limited and the small NE subgroups might have led to inability to a type II error, or inability to detect a difference in cerebral abnormalities detected by MRI. It may be suggested that the incidence of MRI abnormalities found in infants with mild NE simply reflects that of the general population without NE. This is very unlikely, as previously reported MRI data on healthy newborns has shown the prevalence of any abnormality on MRI among healthy controls to be <10%, with no infants having a moderate-severe MRI abnormality.[33] In addition, the rates of moderate-severe cerebral injury among those with moderate (17%) and severe NE (33%) reported here are consistent with recent reports of infants with moderate-severe NE following TH. For example, Bonficaio et al reported moderate-severe injury in 34% [12/35],[24] and Skranes et al reported moderate-severe injury in 17% [7/41] of infants with moderate-severe NE,[25] indicating that our sample could be generally representative of the current burden of MRI injury among infants with moderate-severe NE. An additional limitation of our study is the lack of long-term follow-up on our population, as standardized neurodevelopmental assessment remains the gold standard for outcome in these infants. Despite this, moderate-severe MRI abnormalities have been repeatedly shown to be a robust surrogate predictor of long-term outcome following TH.[34, 35] Additionally, the rates of moderate-severe MRI abnormality in our sample are cons i s tent with the rates of significant long-term neuro-developmental deficits reported among infants with mild NE in alternate studies.[19, 28] Lastly, it is notable that eight infants with mild NE had seizures during their hospital course, which may suggest more significant clinical severity of NE. However, the frequency of seizures in our mild NE group is consistent with previous studies of infants with mild NE.[11] Additionally, Robertson and Finer reported that 48% of infants with mild NE in their cohort had seizures during the newborn period and were continued to be classified as mild NE unless their clinical neurological examination deteriorated.[1] A repeat of our own analysis reclassifying these 8 cases as moderate NE, did not change our results (data not shown).

In conclusion, we report high rates of MRI cerebral abnormalities among infants with mild NE. We could not find in our sample any difference in the frequency of moderate-severe MRI cerebral injury between those with mild or more severe grades of NE. Although the significance of milder MRI abnormalities for long-term outcome is unclear, there is a strong association between moderate-severe MRI injuries and long-term neurodevelopmental deficits.[34, 35] Infants with mild NE deserve greater focus and future investigation, with particular emphasis on the potential benefits of neuroprotective strategies.

Acknowledgments

Funded by NIH (5 T32 HD 7466-18 [to B.W.]).

Abbreviations

MRI Magnetic resonance imaging

References

1. Robertson C, Finer N. Term infants with hypoxic-ischemic encephalopathy: outcome at 3.5 years. Dev Med Child Neurol. 1985; 27:473–84. [PubMed: 4029517]
2. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. The Cochrane database of systematic reviews. 2013; 1:CD003311.
3. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. The New England journal of medicine. 2009; 361:1349–58. [PubMed: 19797281]
4. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. The New England journal of medicine. 2005; 353:1574–84. [PubMed: 16221780]
5. van de Riet JE, Vandenbussche FP, Le Cessie S, Keirse MJ. Newborn assessment and long-term adverse outcome: a systematic review. Am J Obstet Gynecol. 1999; 180:1024–9. [PubMed: 10203673]
6. Azzopardi D, Strohm B, Linsell L, Hobson A, Juszczak E, Kurinczuk JJ, et al. Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK--analysis of national data. PLoS One. 2012; 7:e38504. [PubMed: 22719897]
7. Massaro AN, Murthy K, Zaniletti I, Cook N, DiGeronimo R, Dizon M, et al. Short-term outcomes after perinatal hypoxic ischemic encephalopathy: a report from the Children's Hospitals Neonatal Consortium HIE focus group. Journal of perinatology : official journal of the California Perinatal Association. 2015; 35:290–6. [PubMed: 25393081]
8. Kracer B, Hintz SR, Van Meurs KP, Lee HC. Hypothermia therapy for neonatal hypoxic ischemic encephalopathy in the state of California. The Journal of pediatrics. 2014; 165:267–73. [PubMed: 24929331]
9. Volpe, JJ. Neurology of the newborn. 5th. Philadelphia: Saunders/Elsevier; 2008.
10. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976; 33:696–705. [PubMed: 987769]
11. DuPont TL, Chalak LF, Morriss MC, Burchfield PJ, Christie L, Sanchez PJ. Short-term outcomes of newborns with perinatal acidemia who are not eligible for systemic hypothermia therapy. The Journal of pediatrics. 2013; 162:35–41. [PubMed: 22871488]
12. van Handel M, Swaab H, de Vries LS, Jongmans MJ. Behavioral outcome in children with a history of neonatal encephalopathy following perinatal asphyxia. J Pediatr Psychol. 2010; 35:286–95. [PubMed: 19542199]

13. Lally PJ, Price DL, Pauliah SS, Bainbridge A, Kurien J, Sivasamy N, et al. Neonatal encephalopathic cerebral injury in South India assessed by perinatal magnetic resonance biomarkers and early childhood neurodevelopmental outcome. PLoS One. 2014; 9:e87874. [PubMed: 24505327]
14. Murray DM, O'Connor CM, Ryan CA, Korotchikova I, Boylan GB. Early EEG Grade and Outcome at 5 Years After Mild Neonatal Hypoxic Ischemic Encephalopathy. Pediatrics. 2016
15. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet (London, England). 2005; 365:663–70.
16. White CR, Doherty DA, Henderson JJ, Kohan R, Newnham JP, Pennell CE. Accurate prediction of hypoxic-ischaemic encephalopathy at delivery: a cohort study. J Matern Fetal Neonatal Med. 2012; 25:1653–9. [PubMed: 22233402]
17. Walsh BH, Boylan GB, Livingstone V, Kenny LC, Dempsey EM, Murray DM. Cord blood proteins and multichannel-electroencephalography in hypoxic-ischemic encephalopathy. Pediatr Crit Care Med. 2013; 14:621–30. [PubMed: 23823198]
18. Wiberg N, Kallen K, Herbst A, Olofsson P. Relation between umbilical cord blood pH, base deficit, lactate, 5-minute Apgar score and development of hypoxic ischemic encephalopathy. Acta Obstet Gynecol Scand. 2010; 89:1263–9. [PubMed: 20846059]
19. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. Arch Pediatr Adolesc Med. 2011; 165:692–700. [PubMed: 21464374]
20. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics. 1999; 103:1263–71. [PubMed: 10353940]
21. Strohm B, Hobson A, Brocklehurst P, Edwards AD, Azzopardi D, Register UTC. Subcutaneous fat necrosis after moderate therapeutic hypothermia in neonates. Pediatrics. 2011; 128:e450–2. [PubMed: 21727110]
22. Barkovich AJ, Hajnal BL, Vigneron D, Sola A, Partridge JC, Allen F, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. AJNR American journal of neuroradiology. 1998; 19:143–9. [PubMed: 9432172]
23. Chakkarapani E, Poskitt KJ, Miller SP, Zwicker JG, Xu Q, Wong DS, et al. Reliability of Early Magnetic Resonance Imaging (MRI) and Necessity of Repeating MRI in Noncooled and Cooled Infants With Neonatal Encephalopathy. J Child Neurol. 2016; 31:553–9. [PubMed: 26323498]
24. Bonifacio SL, Glass HC, Vanderpluym J, Agrawal AT, Xu D, Barkovich AJ, et al. Perinatal events and early magnetic resonance imaging in therapeutic hypothermia. The Journal of pediatrics. 2011; 158:360–5. [PubMed: 20965514]
25. Skranes JH, Cowan FM, Stiris T, Fugelseth D, Thoresen M, Server A. Brain imaging in cooled encephalopathic neonates does not differ between four and 11 days after birth. Acta paediatrica (Oslo, Norway : 1992). 2015; 104:752–8.
26. Gagne-Loranger M, Sheppard M, Ali N, Saint-Martin C, Wintermark P. Newborns Referred for Therapeutic Hypothermia: Association between Initial Degree of Encephalopathy and Severity of Brain Injury (What About the Newborns with Mild Encephalopathy on Admission?). Am J Perinatol. 2016; 33:195–202. [PubMed: 26352683]
27. Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. Pediatrics. 2009; 124:e459–67. [PubMed: 19706569]
28. Zhou WH, Cheng GQ, Shao XM, Liu XZ, Shan RB, Zhuang DY, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in China. The Journal of pediatrics. 2010; 157:367–72. 72 e1–3. [PubMed: 20488453]
29. Kontio T, Toet MC, Hellstrom-Westas L, van Handel M, Groenendaal F, Stjerna S, et al. Early neurophysiology and MRI in predicting neurological outcome at 9–10 years after birth asphyxia. Clin Neurophysiol. 2013; 124:1089–94. [PubMed: 23403266]
30. Fatemi A, Wilson MA, Johnston MV. Hypoxic-ischemic encephalopathy in the term infant. Clin Perinatol. 2009; 36:835–58. vii. [PubMed: 19944838]

31. Chevallier M, Ego A, Cans C, Debillon T, French Society of N. Adherence to hypothermia guidelines: a French multicenter study of fullterm neonates. PLoS One. 2013; 8:e83742. [PubMed: 24391817]

32. Wang B, Armstrong JS, Reyes M, Kulikowicz E, Lee JH, Spicer D, et al. White matter apoptosis is increased by delayed hypothermia and rewarming in a neonatal piglet model of hypoxic ischemic encephalopathy. Neuroscience. 2016; 316:296–310. [PubMed: 26739327]

33. Cahill AMG, McKinstry R, Smyser C, Mathur A. Brain injury in term-born infants: does acidemia select those at risk? American Journal of Obstetrics & Gynecology. 2015; 212

34. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. The Lancet Neurology. 2010; 9:39–45. [PubMed: 19896902]

35. Martinez-Biarge M, Diez-Sebastian J, Kapellou O, Gindner D, Allsop JM, Rutherford MA, et al. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurology. 2011; 76:2055–61. [PubMed: 21670434]

Table 1

Local Inclusion criteria for Therapeutic Hypothermia

A. >34 weeks' gestation

AND

B. **<u>One</u> of the following;**

- **a.** Sentinel event prior to delivery
- **b.** Apgar score ≤ 5 at 10 minutes
- **c.** Prolonged resuscitation at birth- chest compressions and/or intubation and/or positive pressure ventilation at 10 minutes
- **d.** pH ≤ 7.1 from cord blood gas or blood gas within the first hour after birth
- **e.** Base excess > −12 mEq/L from cord blood gas or blood gas within the first hour after birth

AND

C. **<u>One</u> of the following;**

- **a.** Seizure or any clinical concern for seizure
- **b.** Neonatal encephalopathy

Table 2

Grading system of MRI injury Shaded area represents moderate-severe MRI injury in dichotomized outcome

Basal Ganglia/Thalamus		**Watershed**	
Score		**Score**	
0	**Normal or isolated focal cortical infarct**	**0**	**Normal**
1	Abnormal signal in the thalamus	**1**	Single focal infarction
		2	Abnormal signal in anterior or posterior watershed white matter
2	Abnormal signal in the thalamus and lentiform nucleus	**3**	Abnormal signal in anterior or posterior watershed cortex and white matter
3	Abnormal signal in the thalamus, lentiform nucleus, and perirolandic cortex	**4**	Abnormal signal in both anterior and posterior watershed zones
4	More extensive involvement	**5**	More extensive cortical involvement

Table 3

Demographic, Perinatal and Clinical Details

	Mild NE	Moderate NE	Severe NE	*Post-Hoc Analysis*			
Demographics	**(n=48)**	**(n=35)**	**(n=6)**	***p value***	***Mild v Moderat***	***Mild v Sever***	***Moderate v Severe***
Gestation (weeks)	39.5 (38.6–40.4)	38.8 (37.4–40.4)	38.6 (37.3–40.5)	0.53			
Birth Weight (gm)	3268 (2968–3548)	3245 (2810–3555)	3247 (2775–3835)	0.98			
Birth wt <10%ile	6 (12%)	3 (8%)	0	0.38			
Sex (M/F)	26/22 (54/46)	19/16 (54/46)	5/1 (83/17)	0.38			
Inborn	29 (60)	22 (63)	4 (67)	0.9			
Method of Delivery				0.17			
SVD	13 (27)	9 (26)	2 (33)				
Instrumental	11 (23)	2 (6)	0				
Emergent Cesarean	24 (50)	24 (69)	4 (67)				
Perinatal Data							
Resuscitation required	41 (85)	31 (89)	6 (100)	0.6			
Perinatal event	22 (47)	16 (46)	4 (67)	0.63			
First pH	7.09 (6.98–7.27)	7.08 (6.96–7.22)	6.93 (6.66–7.06)	0.17			
First BE	−11.2 (−6.0 to −14.5)	−12.5 (−7.8 to −17.4)	−14.9 (−7.0 to −24.4)	0.22			
Highest Lactate	4.5 (2.6–7.9)	5.9 (2.7–10.3)	5.7 (3.8–13.9)	0.32			
Apgar at 10 min < 5	6 (13)	9 (26)	3 (50)	0.17			
PPV Required at 10 min	11 (23)	14 (40)	6 (100)	**0.001**	0.15	<**0.001**	0.009

	Mild NE	Moderate NE	Severe NE	*Post-Hoc Analysis*			
Demographics	**(n=48)**	**(n=35)**	**(n=6)**	***p value***	***Mild v Moderat***	***Mild v Sever***	***Moderate v Severe***
aEEG± Applied (n)	36	27	5	**0.001**	0.18	**<0.001**	0.03
Normal/Mild	26 (72)	14 (52)	2 (40)				
Moderate	9 (25)	10 (37)	0				
Severe	1 (3)	3 (11)	3 (60)				
Age at NE Exam (hr)	4 (2–5)	2.5 (1–4)	2 (1.9–3.1)	**0.007**	**0.004**	**0.87**	0.051
Timing of MRI scans							
First MRI- Day of life	4 (4–5)	4 (3–5)	4 (2–7)	**0.72**			
First MRI- PMA (week)	40.1 (39.0–40.9)	39.2 (37.6–40.8)	39.1 (37.6–41.1)	**0.39**			
Second MRI- Day of life	12 (9–14)	13 (10–17)	11 (9–13)	**0.28**			
Second MRI- PMA (week)	40.9 (39.1–41.9)	41.3 (38.7–42.3)	39.9 (37.1–40.0)	**0.25**			
Short Term Outcome							
Anemia	3 (7)	3 (9)	1 (17)	**0.02**	1.0	0.4	0.5
Leukopenia	1 (2)	2 (6)	1 (17)	0.48			
Thrombocytopenia	13 (29)	17 (52)	2 (33)	0.19			
Highest PT recorded	17 (16–18)	19 (17–21)	20 (17–23)	**0.05**	0.037	0.09	0.52
Highest INR recorded	1.4 (1.3–1.5)	1.5 (1.4–1.8)	1.7 (1.4–2.1)	**0.04**	0.032	0.08	0.47
Highest PTT recorded	44 (38–52)	51 (42–61)	52 (44–74)	0.09			
Received Blood Product	8 (17)	16 (46)	6 (100)	**<0.001**	**0.004**	**<0.001**	0.02
PRBC	2 (4)	8 (23)	3 (50)	**0.004**	**0.01**	**0.007**	0.3

J Pediatr. Author manuscript; available in PMC 2018 August 01.

	Mild NE	Moderate NE	Severe NE	*Post-Hoc Analysis*			
Demographics	**(n=48)**	**(n=35)**	**(n=6)**	***p value***	***Mild v Moderat***	***Mild v Sever***	***Moderate v Severe***
Platelets	2 (4)	8 (23)	2 (33)	**0.03**	**0.01**	0.06	0.6
FFP or Cryoprecipitate	6 (13)	12 (34)	5 (83)	**<0.001**	**0.017**	**0.001**	0.06
Major hemorrhage‡	0	1	1	0.07			
Significant arrhythmia	0	0	0	1.0			
Fat necrosis	1	1	0	0.95			
Ventilated	8 (17)	13 (37)	6 (100)	**<0.001**	**0.007**	**<0.001**	**0.006**
Duration of ventilation	0 (0–8)	0 (0–12)	7 (1–13)	**<0.001**	**0.033**	**<0.001**	**0.002**
(days) †							
Required Inotrope	1 (2)	8 (23)	3 (50)	**0.001**	**0.003**	**0.003**	0.3
Seizures	8 (17)	8 (23)	4 (67)	0.057			
Clinical only	2	6	2				
Electro-clinical	5	2	1				
Electrical only	1	0	0				
Time of 1st seizure (HOL)	10.5 (6–52)	1.6 (1–13)	2 (1–4)				
AED at discharge	3 (6)	2 (6)	1 (17)	0.76			
Achieved full enteral	6 (5–7)	7 (5–9)	6 (4–6)	0.13			
feeds (days)							
NG/GT feed at discharge	0	0	2 (33)	**<0.001**			
Length of stay (days)	8 (6–12)	11 (7–13)	11 (5–33)	0.24			

	Mild NE	Moderate NE	Severe NE	*Post-Hoc Analysis*			
Demographics	**(n=48)**	**(n=35)**	**(n=6)**	***p value***	***Mild v Moderat***	***Mild v Sever***	***Moderate v Severe***
Death	0	2 (6)	1 (17)	0.11			

Data are displayed as median (IQR),

†(Min –Max), n (%). Analysis across groups were performed using a Kruskall-Wallis H Test or Chi Squared. For Post-Hoc analysis Mann Whitney U test or Fisher's exact test were used, as appropriate. A Bonferroni correction was applied to post-hoc analysis, for which significance was taken as $p < 0.016$

*± not all infants had an aEEG- applied in 36 infants with mild NE, 27 with moderate NE, and 5 with severe NE

Definitions: SVD- spontaneous vaginal delivery, BE- Base excess, PMA- post-menstrual age, PRBC- packed red blood cells, FFP- Fresh frozen plasma, AED- Antiepileptic medications, NG- Nasogastric tube, GT- Gastric Tube, Thrombocytopenia- platelet count <150000, Anemia- hematocrit <30, Leucopenia- white blood cell count$<5 \times 10^9$, Major hemorrhage - bleeding necessitating immediate transfusion of product, Perinatal event- uterine rupture, shoulder dystocia, cord prolapse or fetal bradycardia

Table 4

Association between MRI abnormalities and grade of Neonatal Encephalopathy

	Mild NE (n=48)	Moderate NE (n=35)	Severe NE (n=6)	*p* value
Normal	22 (46)	16 (46)	3 (50)	0.98
Isolated IVH	4 (8)	1 (3)	0	0.46
Isolated Cerebellar Hemorrhage	2 (4)	2 (6)	0	0.81
Isolated Sinus Venous Thrombosis	0	1 (3)	0	
Punctate white matter lesion	2 (4)	2 (6)	0	0.81
Injury Consistent with Barkovich Classification	18 (38)	13 (37)	3 (50)	0.83
Basal Ganglia/Thalamic Injury	2 (4)	3 (9)	2 (34)	0.032
Severity of Basal Ganglia/Thalamic Injury †				
1. Abnormal signal in the thalamus	*2 (4)*			
2. Abnormal signal in the thalamus and lentiform nucleus		*1 (3)*	*1 (17)*	
3. Abnormal signal in the thalamus, lentiform nucleus, and perirolandic cortex *4. More extensive involvement*		*2 (6)*	*1 (17)*	
Watershed Injury	18 (36)	11 (32)	3 (50)	0.33
Severity of Watershed Injury †				
1. Single focal infarction	*4 (8)*	*3 (9)*		
2. Abnormal signal in anterior or posterior watershed white matter	*3 (6)*	*4 (11)*	*2 (33)*	
3. Abnormal signal in anterior or posterior watershed cortex and white matter	*5 (10)*	*2 (6)*		
4. Abnormal signal in both anterior and posterior watershed zones	*5 (10)*	*1 (3)*		
5. More extensive cortical involvement	*1 (2)*	*1 (3)*	*1 (17)*	
Moderate-Severe Injury on MRI †	11 (23)	6 (17)	2 (33)	0.62

n (%). Analysis across groups was performed using the Chi Squared test.

† Severity of injury defined using Barkovich grading system as detailed in methods section