The Frequency and Severity of Magnetic Resonance Imaging Abnormalities in Infants with Mild Neonatal Encephalopathy

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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 retrospective cohort studied infants with mild, moderate, and severe neonatal encephalopathy who received therapeutic hypothermia at a single tertiary neonatal intensive care unit between 2013 and 2015. Two neuroradiologists masked to the clinical condition evaluated brain MRIs for cerebral injury after therapeutic hypothermia 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 neonatal encephalopathy.

Results Eighty-nine infants received therapeutic hypothermia and met study criteria, 48 with mild neonatal encephalopathy, 35 with moderate neonatal encephalopathy, and 6 with severe neonatal encephalopathy. Forty-eight infants (54%) had an abnormality on MRI. There was no difference in the rate of overall MRI abnormalities by grade of neonatal encephalopathy (mild neonatal encephalopathy 54%, moderate neonatal encephalopathy 54%, and severe neonatal encephalopathy 50%; $P = .89$). Basal ganglia/thalamic injury was more common in those with severe neonatal encephalopathy (mild neonatal encephalopathy 4%, moderate neonatal encephalopathy 9%, severe neonatal encephalopathy 34%; $P = .03$). In contrast, watershed injury did not differ between neonatal encephalopathy grades (mild neonatal encephalopathy 36%, moderate neonatal encephalopathy 32%, severe neonatal encephalopathy 50%; $P = .3$).

Conclusion Mild neonatal encephalopathy is commonly associated with MRI abnormalities after therapeutic hypothermia. The grade of neonatal encephalopathy during the first hours of life may not discriminate adequately between infants with and without cerebral injury noted on MRI after therapeutic hypothermia. *(J Pediatr 2017;187:26-33).*

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

Mild neonatal encephalopathy has previously been considered a benign clinical syndrome with a good long-term prognosis.[1,5] For this reason, and owing to concerns about the potential side effects of therapeutic hypothermia, infants with mild neonatal encephalopathy were not eligible for the previous RCTs. However, there has been an increasing trend to provide therapeutic hypothermia to newborns with mild neonatal encephalopathy.[6-8] There are several potential explanations for this. First, the clinical examination evolves over time after brain injury,[9,10] such that a single examination within the first 6 hours of life may not reflect the full extent of injury.[1,10] Second, although the morbidity associated with mild neonatal encephalopathy 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 neonatal encephalopathy who underwent therapeutic hypothermia. Therefore, this study aimed to describe the magnetic resonance imaging (MRI) findings in infants with mild neonatal encephalopathy after therapeutic

EEG	Electroencephalography
MRI	Magnetic resonance imaging
RCT	Randomized, controlled trial
TE	Echo times
TR	Repetition time

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hypothermia and to compare the severity of cerebral injury defined on MRI with that of infants with moderate or severe neonatal encephalopathy after therapeutic hypothermia.

Methods

This retrospective cohort study included all infants who underwent therapeutic hypothermia between September 2013 and December 2015 in a single tertiary level neonatal intensive care unit. Institutional review board approval was obtained. The inclusion criteria for therapeutic hypothermia 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 owing to concerns regarding the poor specificity of some of the RCT variables for neonatal encephalopathy,[16-18] along with recognition of greater morbidity in mild neonatal encephalopathy.[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 therapeutic hypothermia to infants with mild neonatal encephalopathy on clinical examination, in addition to those with moderate or severe neonatal encephalopathy (**Table I**). All infants in this study were born after the change in the local criteria. The inclusion criteria required that therapeutic hypothermia be initiated within the first 6 hours of life, in keeping with the RCTs. Infants with confounding conditions that may have resulted independently in abnormalities on the cerebral MRI were excluded from this analysis.

The clinical grade of encephalopathy was assigned after combined assessment by both a child neurologist and neonatologist. The grade of neonatal encephalopathy was defined as either mild, moderate, or severe, based on a well-validated, standardized neurologic examination.[4,10] The initial neurologic assessment performed in the first hours of life before the initiation of hypothermia is used herein when defining severity of encephalopathy.

After clinical assessment and encephalopathy grading, amplitude-integrated electroencephalography (EEG) monitoring was initiated, typically within the first hours of life. This was performed using either an Olympic Cerebral Function Monitor 6000 or an Olympic Brainz (Natus, San Antonio, California), and was graded prospectively using the amplitude classification system described by al Naqeeb et al.[20] The amplitude-integrated EEG monitoring was transitioned to continuous multichannel video EEG after the initiation of therapeutic hypothermia and remained in place for the duration of hypothermia and rewarming. The continuous multichannel video EEG recordings were reviewed for the presence and timing of electrical seizures. This information was not a part of the clinical assessment of severity of neonatal encephalopathy. However, the data were used in this cohort for secondary analysis to assess whether reclassifying mild infants with seizure activity into the moderate neonatal encephalopathy category influenced the primary results and whether the incorporation of background pattern on amplitude-integrated EEG 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 therapeutic hypothermia that were identified from the literature,[2,21] 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.

Table I. Local inclusion criteria for therapeutic hypothermia

A. >34 weeks of gestation
AND
B. One of the following;
   a. Sentinel event before 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 min
   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. One of the following;
   a. Seizure or any clinical concern for seizure
   b. Neonatal encephalopathy

Magnetic Resonance Imaging

All infants underwent at least 1 cerebral MRI performed after therapeutic hypothermia 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 seemed 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 neonatal encephalopathy.

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 T1-weighted images (repetition time [TR] of 2800 ms, echo times [TE] of 2.75, 4.68, 6.54, and 8.4 ms, flip angle 7°, voxel size of $1 \times 1 \times 1$ mm), axial turbo spin echo T1-weighted images (TR of 574 ms, TE of 13 ms, flip angle 140°, voxel size of $0.5 \times 0.5 \times 3$ mm, echo train length of 2), axial turbo spin echo T2-weighted images (TR of 9000 ms, TE of 150 ms, flip angle 120°, voxel size of $0.5 \times 0.5 \times 3$ mm, echo train length of 19), and coronal turbo spin echo T2-weighted images (TR of 9210 ms, TE of 187 ms, flip angle 130°, voxel size of $0.4 \times 0.4 \times 3$ mm, echo train length of 19).