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Original Article

Early Anatomical Injury Patterns Predict Epilepsy in Head Cooled Neonates With Hypoxic-Ischemic Encephalopathy

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ABSTRACT

BACKGROUND: Our aim was to determine whether early anatomical injury patterns on magnetic resonance imaging-correlate with the development of postneonatal epilepsy in infants treated with selective head cooling for hypoxic-ischemic encephalopathy. **METHODS:** We retrospectively analyzed infants ≥35 weeks' gestation born between 2008 and 2013 and followed for at least one year at Northwestern University. All had brain magnetic resonance imaging scans at days 4-5 and electroencephalographs during rewarming and at 3 to 6 months of age. **RESULTS:** Outcome was favorable for our cohort of 73 individuals with a mean follow-up of 41 (±7) months. The majority (66%) survived with no seizure recurrence, whereas 13 (18%) developed postneonatal epilepsy, including eight who had infantile spasms. Twelve infants (16%) died. The most common magnetic resonance imaging pattern was diffuse brain injury involving both cortical and subcortical gray matter (26/73, 35%), followed by cortical and subcortical white matter injury (18/73, 25%) and normal magnetic resonance imaging (16/73, 22%). In 13 infants (18%), the brainstem was involved in addition to cortical and subcortical gray matter; nine died and all four surviving infants developed infantile spasms. All 18 infants with cortical and subcortical white matter injury survived and none developed postneonatal epilepsy. The risk of postneonatal epilepsy was associated with injury involving subcortical regions (basal ganglia, thalamus ± brainstem) (12/39 versus 1/34, $P < 0.003$). **CONCLUSIONS:** Brainstem injury was highly predictive of infantile spasms, whereas cortical injury alone predicted low risk for short-term postneonatal epilepsy. Location of anatomical injury on magnetic resonance imaging can be an early predictive factor for development of infantile spasms and inform prognostic decisions in newborns treated with selective head cooling for hypoxic-ischemic encephalopathy.

Keywords: hypoxic-ischemic injury, neonatal seizures, hypothermia, infantile spasms, postneonatal epilepsy, magnetic resonance images, epilepsy

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Introduction

Hypoxic-ischemic encephalopathy (HIE) affects 1 to 6 per 1000 live births.[1] Therapeutic hypothermia using selective head or whole body cooling has been shown to improve neurodevelopmental outcome of infants with HIE.[2–4] Although this effect is most pronounced in infants with moderate HIE,[5,6] there is some evidence that infants with severe HIE also have improved outcomes with cooling.[4] Less hypoxic injury is seen on magnetic resonance imaging (MRI) after cooling, but there may be differences in the radiographic extent of injuries with selective head versus whole body cooling.[7,8]

Numerous studies have shown that seizures occur frequently with HIE at presentation, during cooling, and with rewarming. The Cool Cap Study (selective head cooling) reported seizures in 60% of infants,[2] whereas a whole body cooling study found that 45% of infants had seizures at time of enrollment.[3] During or immediately following

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hypothermia, electrographic or clinical seizures were noted in 30% to 90% of infants.[9–12] Although seizures are common presenting signs of HIE, development of epilepsy following therapeutic hypothermia is not well characterized. Studies before the institution of cooling found that approximately 7% to 16% of infants with moderate HIE developed epilepsy and that the rate was significantly higher (up to 60%) for infants with severe injury.[13–17]

Presently, little is known about the incidence of epilepsy in infants treated with selective head cooling for HIE. The same is true regarding whether early MRI features can predict epilepsy development. A previous study that evaluated whole body cooled and noncooled infants showed that there was a correlation between location of injury and development of infantile spasms.[18] The objective of this study was to categorize MRI patterns of injury in infants treated with selective head cooling following HIE between 2008 and 2013 at Northwestern University and to determine whether early anatomical injury patterns on MRI can be correlated with the development of postneonatal epilepsy (PNE). PNE was defined as recurrent, unprovoked seizures that were present after the neonatal period (greater than 28 days).[15,19,20]

Methods

This was a retrospective single-center cohort study. The Institutional Review Board at Lurie Children's Hospital approved the study, including waiver of consent. We reviewed records for all infants treated for HIE with selective head cooling who were treated between August 2008 and May 2013 at two hospitals affiliated with Northwestern University: Prentice Women's Hospital and Anne & Robert H Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital). All infants had moderate to severe asphyxia, fulfilling the clinical entry criteria that were used in the Cool Cap trials.[2,21]

The institutional inclusion criteria for selective head cooling treatment requires meeting criteria A and one of the three components of criteria B.

Criteria A: Infants older than 35 weeks' gestation admitted with one or more of the following: (1) Apgar score of <5 at 10 minutes after birth; (2) continued resuscitation (endotracheal or mask) at 10 minutes after birth; (3) acidosis (pH < 7.00 of cord blood or arterial blood < 60 minutes of life); or (4) base deficit ≥16 mmol/L in cord blood or any blood < 60 minutes of life.

Criteria B: (1) Moderate to severe encephalopathy, with altered level of consciousness and at least one of the following: lethargy, stupor or coma, hypotonia, abnormal reflexes including oculomotor or pupillary abnormalities, and absent or weak suck; (2) clinical seizures; or (3) at least 20 minutes of amplitude-integrated electroencephalograph with moderately abnormal or suppressed background amplitude[22] or seizures, after 1 hour of age.

Exclusion criteria for selective head cooling were: (A) Major congenital abnormalities, including brain dysgenesis; (B) evidence of head trauma or skull fracture; or (C) markedly small size (infants < 1800 grams birth weight, head circumference >2 standard deviations below mean for gestation).

Patient population

Eighty-six infants underwent selective head cooling. Of these, 13 were excluded: four with congenital heart disease, one with brain malformation, one with chromosomal anomaly, three who did not undergo MRI, and four who were lost to follow-up before 12 months. Of the 73 infants analyzed for this study, two were cooled at 34 4/7 weeks' gestation and four were cooled at 35 weeks' gestation. All infants were followed by one of the authors (CV or DR) at least three times during first 18 months of life (at 6 weeks to 3 months, 4 to 6 months, and 12 to 18 months). Only those infants who had neurological follow-up for at least 1 year were included in the study (mean ± standard deviation; 41 ± 7 months).

At the initiation of cooling, clinical seizures and subclinical seizures detected on amplitude-integrated electroencephalograph tracings were treated with antiepileptic medication. No electroencephalography or amplitude-integrated electroencephalography monitoring was performed during the cooling period given technical constrains with the cooling cap in place; therefore, only clinical seizures were treated during cooling. During the rewarming period, neonates were monitored using conventional video-electroencephalography. Antiepileptic drug treatment was directed by the neonatology department with input from consulting neurologists. Typically, the first-line medication was phenobarbital followed by fosphenytoin, if necessary. Conventional video-electroencephalography data from the rewarming period were not available for all infants enrolled in this retrospective study. Therefore, we did not analyze electroencephalography data and patterns of early seizures for this study.

Follow-up electroencephalography was obtained at 3 months and, if abnormal, at about 6 months of age. Subsequent electroencephalographs were obtained if clinically indicated. Electroencephalography interpretations were performed by board-certified neurophysiologists at Northwestern University.

MRI scans were performed on day of life 4 or 5 and were reviewed by board-certified neuroradiologists at Northwestern University. The following sequences were optimized for the neonatal brain at this institution, as described previously.[23–26] Three-dimensional T1-weighted spoiled gradient-echo sequence, T2-weighted fast spin-echo sequence, fluid-attenuated inversion recovery, and diffusion-weighted imaging were performed with an axial multisection multirepetition spin-echo echo-planar technique. Diffusion-weighted imaging was acquired in three orthogonal directions and combined into a trace image. Apparent diffusion coefficient map was calculated by using the b-values of 0 and 1000 s/mm^2 on a voxel-by-voxel basis with the software incorporated into the MRI unit. Newborns were grouped into four patterns of injury on the basis of the predominant anatomical site of injury on MRI using a modified scheme published in other studies found to be predictive of neurodevelopmental outcome after neonatal encephalopathy:[23,26] (1) normal; (2) cortex injury alone; (3) cortex and basal ganglia/thalamus injury; or (4) cortex, basal ganglia/thalamus and brainstem injury. Review of MRIs and scoring of injury was performed by DEJ and SK, who were blinded to clinical outcome of the patients.

Statistics

Statistical analyses were performed using statistical software (SPSS, version 21.0, SPSS, Chicago, IL, USA). The $\chi 2$ and Fisher exact tests were used to compare dichotomous variables, and the Student *t* test was used for continuous variables. The Wilcoxon rank-sum test (or Mann-Whitney *U* test) was used to compare nonparametric data. A P value ≤0.05 was considered significant.

Results

Patients

The cohort consisted of 73 patients selected from 86 newborns who had undergone selective head cooling for HIE during the catchment period between 2008 and 2013. These infants were followed for at least 1 year (mean: 41 ± 7 months). There were 43 male (59%) and 30 female (41%). Twelve neonates (16%) died during the initial hospitalization.

Radiographic imaging features

MRI scans were performed on day 4 or 5 of life. The most common pattern of injury involved both cortical and