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

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Abstract

OBJECTIVE—To determine whether early anatomical injury patterns in MRI correlate with the development of post-neonatal epilepsy in infants treated with selective head cooling for hypoxic ischemic encephalopathy.

STUDY DESIGN—A retrospective study of infants   35 weeks' gestation born between 2008 and 2013 and followed for at least one year at Northwestern University. All had brain MRI at day 4–5 and EEGs during rewarming and at 3 to 6 months of age.

RESULTS—Outcome was favorable for our cohort of 73 with mean follow-up of 41 ($\pm$ 7) months. The majority (66%) survived with no seizure recurrence, while 13 (18%) developed post neonatal epilepsy including 8, who had infantile spasms. Twelve infants (16%) died. The most common MRI 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 MRI (16/73, 22%). In 13 infants (18%), the brainstem was involved in addition to cortical and subcortical gray matter; 9 died and all 4 surviving infants developed infantile spams. All 18 infants with cortical and subcortical white matter injury survived and none developed post neonatal epilepsy. Risk of post neonatal epilepsy was associated with injury involving subcortical regions (basal ganglia, thalamus $\pm$ brainstem) (12/39 vs 1/34, *p*<0.003).

CONCLUSIONS—Brainstem injury was highly predictive of infantile spams while cortical injury alone predicted low risk for short term post neonatal epilepsy. Location of anatomical injury on MRI can be an early predictive factor for development of infantile spams 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

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) affects 1 to 6 per 1,000 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] While 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 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] while a whole body cooling study found 45% of infants had seizures at time of enrollment.[3] During or immediately following hypothermia, electrographic or clinical seizures were noted in 30–90% of infants.[9–12] While seizures are common presenting signs of HIE, development of epilepsy following therapeutic hypothermia is not well characterized. Studies prior to the institution of cooling found that approximately 7 – 16 % of infants with moderate HIE developed epilepsy, and 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 non-cooled infants showed that there was a correlation between location of injury and development of infantile spasms (IS)[18]. The objective of this study was to categorize MRI patterns of injury in infants treated with selective head cooling following HIE between 2008–2013 at Northwestern University, and determine whether early anatomical injury patterns on MRI can be correlated with the development of post-neonatal 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 and born 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 greater 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) (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 (3) At least 20 minutes of aEEG with moderately abnormal or suppressed background amplitude[22] or seizures, after one 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. C. Markedly small size (Infants < 1,800 grams birth weight, head circumference >2 SD below mean for gestation).

Patient Population

Eighty six infants underwent selective head cooling. Of these, 13 infants were excluded: 4 with congenital heart disease, one with brain malformation, one with chromosomal anomaly, 3 who did not undergo MRI, and 4 who were lost to follow-up before 12 months. Of the 73 infants analyzed for this study, 2 were cooled at 34 4/7 weeks gestation, and 4 were cooled at 35 weeks gestation. All infants were followed by one of the authors (CV or DR) at least 3 times during first 18 months of life (at 6 weeks – 3 months, 4–6 months and 12–18 months). Only those infants who had neurological follow up for at least one year were included in the study (mean ± SD; 41 ± 7 months).

At the initiation of cooling, clinical seizures and subclinical seizures detected on aEEG tracings were treated with anti-epileptic medication. There was no EEG or aEEG monitoring performed during the cooling period given technical constrains with the cool cap in place and therefore, only clinical seizures were treated during cooling. During the rewarming period, neonates were monitored using conventional video-EEG. Anti-epileptic drug treatment was directed by Neonatology with input from consulting neurologists. Typically, the first line medication used was phenobarbital followed by fosphenytoin, if necessary. Conventional video-EEG data from the rewarming period were not available for all infants enrolled in this retrospective study. Therefore, we did not analyze EEG data and patterns of early seizures for this study.

Follow-up electroencephalography (EEG) was obtained at 3 months and, if abnormal, at about 6 months of age. Subsequent EEGs were obtained if clinically indicated. EEG

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] 3D T1-weighted spoiled gradient-echo sequence, T2-weighted fast spin-echo sequence, Fluid-Attenuated Inversion Recovery (FLAIR), and diffusion-weighted imaging (DWI) were performed with an axial multi-section multi-repetition spin-echo echo-planar technique. DWI was acquired in three orthogonal directions and combined into a trace image. Apparent diffusion coefficient (ADC) map was calculated by using the b-values of 0 and 1000 s/mm2 on a voxel-by-voxel basis with the software incorporated into the MR imaging unit. Newborns were grouped into 4 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 (4) cortex, basal ganglia/thalamus and brainstem injury. Review of MRI images and scoring of injury was performed by D.E.J. and S.K. 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 χ2 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 $\leq$ 0.05 was considered significant.

RESULTS

Patients

The cohort consisted of 73 patients selected from 86 newborns that underwent selective head cooling for HIE during the catchment period between 2008 and 2013. These infants were followed for at least one year (mean: 41($\pm$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 subcortical (basal ganglia and/or thalamus) gray matter (Figure 1A & B) in 26 infants (35%), followed by cortical injury with involvement of the subcortical white matter (Figure 1C & D) in 18 neonates (25%). Cortical injury followed a watershed distribution and there was no single dominant or prevalent pattern of injury. Thus, unilateral or bilateral involvement of one or more regions including frontal, parietal, occipital and temporal areas was evident on MRI scans. Sixteen (22%) infants had normal MRI. The least common pattern, seen in 13 infants (18%), was brainstem involvement in addition to cortical and subcortical gray matter (Figures 1E and 1F).

Development of Post-neonatal Epilepsy

Patients with normal imaging or isolated cortical and white matter injury had the lowest rates of epilepsy (33/34, $p<0.0001$)) (Table 1). Notably, none of the infants with cortical and white matter injury died or developed epilepsy (0/18). Normal MRI, as expected, was also predictive of favorable outcome. All but one infant with normal MRI did well with respect to development of epilepsy (15/16, $p<0.01$). The only infant with normal MRI who developed PNE had abnormal MR spectroscopy, with lactate peak in the CSF, suggesting mild ischemia.

Outcome was more variable in infants with diffuse cortical and subcortical gray matter injury (Table 1). The majority of the surviving neonates with diffuse cortical and subcortical gray matter (BG and Thalamus) injury (58%, $n=15/26$) did not develop epilepsy. However, outcome was worse than in infants with normal MRI or cortical injury alone. In this subset, 3 patients (11%) expired and 8 patients (31%) developed epilepsy, including 4 who developed IS.

Extensive brain injury including the brainstem was highly predictive of unfavorable outcome of either death or infantile spasms (13/13, $p<0.0001$). Nearly 70% (9/13) of infants with brainstem injury died. All surviving infants (4/13) developed infantile spasms (4/4, 100%) within the first 9 months of life (range, 3–9 months; median, 4.5 months). Clinically, this subset of infants who developed IS also had early signs and symptoms of severe brainstem dysfunction, including swallowing dysfunction (requiring placement of gastrostomy tube), respiratory dysfunction (requiring ventilator support or frequent suctioning), encephalopathy, and early development of spasticity, typically by day 21 of life.

DISCUSSION

Therapeutic hypothermia is widely used in the United States for treatment of neonatal hypoxic ischemic injury. While many studies have shown improved neurodevelopmental outcome in cooled infants[2–4], much less is known about the risk of subsequent epilepsy. Our study examined early anatomical injury patterns on MRI in infants treated with selective head cooing for moderate to severe neonatal HIE. Our findings are consistent with previous report of whole body cooled and non-cooled infants in showing that location of injury was predictive of risk of developing PNE, including infantile spasms[18]. In our study, about one third of infants with basal ganglia and/or thalamic lesions developed PNE while all infants with brainstem involvement developed IS. Absence of subcortical involvement indicated relative protection with respect to development of PNE compared to diffuse brain injury including subcortical regions. None of the infants with isolated cortical and subcortical white matter injury developed PNE. Gano et al. found that in whole body cooled and non-cooled babies, brainstem injury was present in 87.5% of infants with infantile spams and 25% of infants without infantile spasms.[18] This supports our finding that head cooled infants with injury to brainstem are at high risk for developing IS.

Technical factors associated with use of Cool Cap for selective head cooling prevent the use of concurrent EEG monitoring during the cooling period. As such, treatment with AEDs during the cooling period was typically based on clinical suspicion of seizures and directed

by the Neonatal team involved in the care of the newborn. Thus, it is possible that subclinical seizures were not detected and treated during the cooling period. It is difficult to speculate how this practice may have impacted MRI findings. The association between acute seizures and extent of brain injury in neonates in the setting of hypothermia has not been fully elucidated. A previous study of neonates with HIE who were treated with hypothermia found that among newborns with seizures, approximately 60% had moderate-severe injury vs. 40% who had mild or no injury [27]. They also found that newborns with subclinical seizures were as likely to have moderate-severe injury as those with clinically apparent seizures [27].

Another limitation is relatively short follow up. To evaluate the onset of PNE, the patients were followed for at least one year (average follow up = 41 months). Although other forms of epilepsy may present later than 12 months of age, IS most often occur before one year of age.[28] Understanding how neonatal HIE leads to epilepsy in later life is an important question in epilepsy research. Although the cortex is often emphasized as the site of seizure origin, epileptic seizures involve widespread network interactions between cortical and subcortical structures, and accumulating evidence points to a crucial role for subcortical structures in propagation and initiation of seizures.[29–31] Previous studies have shown the importance of subcortical structures in animal seizure models, but corresponding human studies, especially in neonates, have been relatively few. Animal models of HIE suggest that post-injury plasticity of the developing brain occurs due to reorganization of thalamocortical, callosal, and intracortical circuitry.[32] Failure to prune immature (possibly epileptogenic) connections following injury due to a hyperinnervated circuitry, may contribute to epilepsy.[32]

There may be a selective neuroprotective effect in the cerebral cortex from hypothermia. Experimental data have shown that glutamate receptor activation, particularly the N-methyl-d- aspartate type, is a critical mediator of selective neuronal injury following HIE in the neonatal brain.[33–35] Mild hypothermia appears to be a potent inhibitor of glutamate release, which may contribute to selectively protecting brain regions that are vulnerable to secondary delayed injury, such as the cerebral cortex.[36] It is also possible that cortical injury seen on DWI sequences on MRI scans represents a transient insult that is not epileptogenic in nature. Selective head cooling may also produce a temperature differential between brain regions, such as the cortex and subcortical gray matter, with a greater reduction in temperature at the surface of the brain rather than in the deep brain structures. Animal experiments have suggested that the variation may be greater in head cooling than systemic cooling[37]; there can be a temperature differential of >6°C between the coldest superficial cortex and subcortical structures in selective head cooling.[38] It is unclear whether this differential temperature variation leads to a greater vulnerability of subcortical structures to ischemic injury in selective head cooling.[39] Our clinical findings encourage future research into the association of subcortical injury and PNE including IS in infants treated with selective head versus whole body cooling for HIE.

Infants with brainstem injury had the worst prognosis, and all surviving infants developed IS. Infantile spasm is an age-specific epileptic encephalopathy characterized clinically by clusters of spasms and a hypsarhythmia pattern on EEG that is most commonly responsive

to treatment with adrenocorticotropic hormone (ACTH) or vigabatrin.[28] Typically, the peak age of occurrence is between 3 and 7 months of age.[28] The underlying pathophysiology and brain structures involved in the generation of IS have not been fully elucidated. There is some evidence that subcortical structures, particularly the midbrain and brainstem may be implicated in its pathogenesis.[39–42] One study compared brains of individuals with HIE who had epilepsy but not IS with those with HIE (or lissencephaly) and IS and noted that only patients with IS had alterations in specific neurotransmitters and neuropeptides in the brainstem.[40] In one study of infants with HIE who did not undergo therapeutic hypothermia, 4.5% developed IS; extensive injury to the basal ganglia/thalamus or total brain injury were found in these patients.[18] Our study found that 100% of infants with whole brain injury that included the brainstem developed IS. This seizure type was noted in 15% of infants with diffuse cortical and subcortical injury including thalamus and basal ganglia. Most important, none of the infants with normal MRI or injury restricted to the cortical mantle and underlying white matter developed IS. This supports the notion that the pathogenesis of IS may involve subcortical structures.

In summary, results of our study show that prognostic information can be gleaned from MRI studies performed on days 4 or 5 of life in selectively head cooled infants with HIE. Injury to brainstem evident on imaging studies and on clinical examination is highly predictive of poor prognosis and development of IS. In contrast, normal MRI or injury limited to cortical surface and the subcortical white matter is predictive of good outcome with respect to the development of PNE.

Acknowledgments

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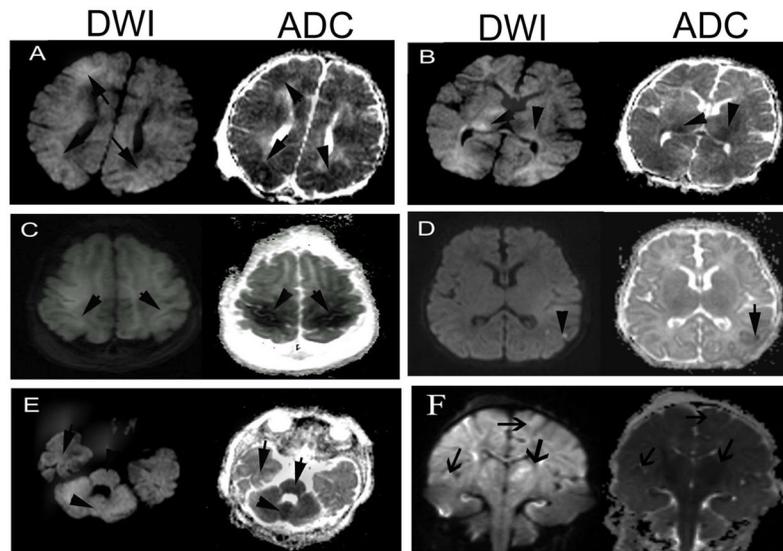
Figure 1. MRI injury patterns in head cooled neonates with HIE

A & **B**: The most common pattern of injury involved the cortical and subcortical gray matter (arrows) in 35% of the infants. **C** & **D**: Isolated cortical injury with subcortical white matter involvement (arrows) was present in 25% of infants. **E and F**: Injury to brainstem, cortical and subcortical structures (arrows) was present in 18% of infants.

DWI= diffusion weighted image and ADC = apparent diffusion coefficient map.

TABLE 1

Anatomical pattern of injury on MRI and outcome in selectively head cooled neonates with hypoxic ischemic injury.

Anatomical pattern of injury on MRI	Survived without PNE	PNE	Infantile spams	Expire	Total
Normal	15	1	0	0	16 (22%)
Cortex and subcortical White matter	18	0	0	0	18 (25%)
Cortex and basal ganglia/thalamus	15	8	4	3	26 (35%)
Cortex, basal ganglia/thalamus and brainstem	0	4	4	9	13 (18%)
Total, n (%)	48 (66%)	13 (18%)	8	12 (16%)	73 (100%)

PNE: Post-neonatal epilepsy; cases include infantile spasms.