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FEarly Glucose Profile is Associated with MRI Brain Injury Patterns in Hypoxic Ischemic Encephalopathy

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Abstract

Objective—To investigate whether the early glycemic profile in infants with hypoxic ischemic encephalopathy (HIE) is associated with distinct brain injury patterns on magnetic resonance imaging (MRI).

Study design—We performed a secondary analysis of 178 prospectively enrolled infants who received therapeutic hypothermia for HIE. Glycemic profiles were identified by glucose concentrations within 24 hours after birth: normoglycemia (all glucose concentrations >47 to 150 mg/dL; n=62); hypoglycemia (1 concentration <47 mg/dL; n=17), hyperglycemia (1 concentration >150 mg/dL; n=76), and labile glucose (both hypoglycemia and hyperglycemia; n=23). Patterns of brain injury were identified for 151 infants based on Barkovich scores from the post-rewarming brain MRIs on median age of 9 days.

Results—Normal brain MRI was reported in 37/62 (60%) infants with normal blood glucose values compared with 37/116 (32%) infants with an abnormal glucose profile (adjusted for Sarnat stage of encephalopathy and Apgar score at 5 minutes, $P=.02$). The distribution of MRI patterns of brain injury differed among the glycemic groups ($P=.03$). Odds of predominant watershed or focal-multifocal injury was higher in infants with hypoglycemia (adjusted OR 6; 95% CI 1.5–24.2) and labile glucose (6.6; 1.6–27) compared with infants with normoglycemia. Infants with

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labile glucose had higher odds (5.6; 1.1–29.3) of predominant basal ganglia or global injury compared with infants with normal blood glucose values.

Conclusion—The early glycemic profile in infants with HIE is associated with specific patterns of brain injury on MRI. Further investigation is needed to explore its prognostic significance and role as a phenotype biomarker.

Keywords

hypoglycemia; hyperglycemia; phenotype; neonatal; hypoxic ischemic encephalopathy; MRI; brain injury pattern; watershed; focal-multifocal infarct; basal ganglia injury

Moderate induced hypothermia treatment has improved survival without disability among infants with hypoxic-ischemic encephalopathy (HIE), yet many treated infants still die or suffer from severe neurodevelopmental and cognitive impairment.^{1–3} It is likely that the heterogeneous mechanisms of HIE as well as chronicity, timing, and severity contribute to this variable response to hypothermia. Identification of early biomarkers of brain injury might provide insight into the specific etiology and underlying pathophysiology and may help to guide individualized neuroprotective interventions to optimize outcomes.

Glucose is the primary substrate for energy metabolism in the newborn brain, and deranged postnatal glucose homeostasis may be either a biomarker or contributor for neuronal injury in infants with HIE.^{4–6} In the CoolCap Study, both hypoglycemia and hyperglycemia were associated with greater risk of an unfavorable outcome.^{7–9} Early glycemic profiles have been related to clinical phenotypes of multi-organ dysfunction and responsiveness to hypothermia and may be associated with patterns of brain injury. Distinct patterns of brain injury on MRI in infants with HIE have been proposed to indicate underlying pathogenesis.^{10–12} For example, although severe hypoglycemia in the setting of neonatal encephalopathy has been associated with parieto-occipital and thalamic injury, it is uncertain if the early postnatal glycemic profile in infants with HIE is associated with distinct MRI brain injury patterns.

We hypothesized that early hypoglycemia in infants with HIE reflects depleted fetal glucose stores and inadequate gluconeogenesis from multi-organ injury due to prolonged partial hypoxia-ischemia and would be associated with the watershed (WS) pattern of brain injury. Conversely, we hypothesized that early hyperglycemia reflects depressed cerebral glucose uptake in the setting of intact gluconeogenesis following an acute hypoxic-ischemic event and would be associated with the basal ganglia (BG) pattern of injury. Moreover, we expect that infants with normal blood glucose values will have the least brain injury. We investigated our hypotheses in a prospectively enrolled cohort of infants with moderate-to-severe HIE treated with whole body hypothermia.

Methods

We enrolled 179 infants with moderate-to-severe HIE who underwent therapeutic hypothermia between 05/2008–04/2016 at a level IV neonatal intensive care unit in a single center prospective observational study evaluating biomarkers of brain injury. Inclusion criteria were based on modified National Institute of Child Health and Human Development

(NICHD) criteria for therapeutic hypothermia: gestational age ≥ 35 weeks, birth weight $\geq 1,800$ grams, metabolic acidosis or low 10-minute Apgar score, and moderate-to-severe encephalopathy on examination based on modified Sarnat criteria. One infant with incomplete postnatal glucose data was excluded from this analysis. Twenty-seven infants died prior to brain MRI. We analyzed detailed glucose data from 178 infants and MRI data from 151 infants in the original prospective observational study in these secondary analyses. Infants were systemically cooled to 33.5°C for 72 hours (Blanketrol II, Cincinnati Sub-Zero, Cincinnati, OH).

Basal glucose infusion rates of 4 mg/kg/min were provided to patients with HIE during the first 24 hours of therapeutic hypothermia per institutional protocol. Blood glucose levels were checked per protocol: on NICU admission, then hourly until stable (50–150 mg/dL) on 2 consecutive specimens, then every 4–6 hours during hypothermia, and as clinically indicated. Insulin was administered for sustained glucose concentrations >200 mg/dL as per standard clinical care guidelines. All glucose concentrations obtained within the first 24 hours, including point-of-care glucometer and routine laboratory measured concentrations were collected. The Institutional Review Board approved the study, and parental informed consent was obtained.

Classification of Early Glycemic Profile

Demographic and clinical data, including laboratory and clinical correlates of multi-organ function, glucose infusion rates during cooling, and death prior to discharge were retrieved from medical records. Infants were classified into 4 glycemic profile groups based on plasma glucose concentrations within the first 24 hours after birth: (1) hypoglycemia only (< 47 mg/dL, < 2.6 mmol/L), (2) hyperglycemia only (> 150 mg/dL, > 8.3 mmol/L), (3) normoglycemia (all glucose concentrations > 47 to < 150 mg/dL, > 2.6 to < 8.3 mmol/L), and (4) labile glucose with both hypoglycemia and hyperglycemia (< 47 mg/dL, < 2.6 mmol/L] and [> 150 mg/dL, > 8.3 mmol/L]).

MRI Patterns of Brain Injury

Post-rewarming brain MRIs were performed on 151 infants per clinical protocol at a median age of 9 (IQR, 7–11) days of age on a 3T scanner (Discovery MR750, GE Healthcare, Milwaukee, WI). Standard anatomical sequences included 3D T1-weighted Spoiled Gradient Recalled, double acquisition axial FSE T2 proton density, axial T2 propeller (in cases of patient motion), axial T2-Star Weighted Susceptibility Imaging, coronal T1 FLAIR propeller, and axial 30-direction DTI with generation of ADC maps off-line. The MRIs were scored according to Barkovich brain injury criteria: (BG [scale 0–4] and WS [scale 0–5]) by a blinded experienced neuroradiologist (GV). MRI scores were grouped into 3 categories for the purposes of statistical analysis as follows: 1) normal; 2) WS (WS $>$ BG score) or focal/multi-focal strokes; and 3) BG (BG $\geq$ WS) or total pattern (WS=5 and BG=4). The primary outcome was defined as the predominant pattern of brain injury on post-rewarming MRI. Secondary analyses were performed including the infants who died prior to MRI as a fourth category.

Statistical Analyses

The demographic, obstetric, and neonatal factors were analyzed with descriptive statistics. Differences among the glycemic groups were assessed with chi-square for categorical variables and ANOVA for continuous variables. We used bivariate tests to identify differences in clinical covariates (with threshold of $P < .1$) among glycemic groups and among MRI patterns of injury. We then used stepwise multinomial logit models to select covariates for the evaluation of multivariate association of glycemic group with MRI patterns of injury. Covariates which remained significant ($P < .05$) were selected for inclusion in the final regression model. Model outputs included odds ratios (OR) with 95% confidence intervals (CI) for the association of glycemic groups and MRI pattern of brain injury with or without adjusting for the selected covariates. All hypothesis tests were two-sided, and statistical significance for the final models was assessed at the .05 level. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

Early Glycemic Profile and Baseline Characteristics

During the first 24 hours, 34.8% (62/178) of infants with moderate-to-severe HIE were normoglycemic and 65.1% (116/178) of infants had 1 abnormal glucose concentration. Demographic and perinatal data stratified by 24-hour glucose profiles are shown in Table I. Infants with normal blood glucose values had higher Apgar scores at 5 and 10 minutes and less need for resuscitation in the delivery room compared with infants with hypoglycemia and hyperglycemia. Severity of encephalopathy by Sarnat stage and frequency of electrographic seizures were lowest among normoglycemic infants.

Indicators of multi-organ dysfunction are summarized in Table II. Infants with hypoglycemia had more biochemical and hematologic laboratory abnormalities compared with infants with normoglycemia and hyperglycemia. Glucose concentration ranges differed among the glycemic profile groups. Average first 24-hour glucose infusion rates were higher among infants with hypoglycemia but not statistically different among the glycemic groups. Also, insulin administration during hypothermia was more common among infants with any hyperglycemia. Among the 33 infants who received insulin for hyperglycemia, 3 infants developed hypoglycemia within first 24 hours and were classified in the labile glucose group. Gestational age, race, maternal diabetes, Sarnat encephalopathy stage at presentation, and Apgar score at 5 minutes met significance criteria on bivariate analyses and were incorporated in the stepwise regression models. Only Sarnat stage of encephalopathy and Apgar score at 5 minutes remained consistently significant ($P < .05$) across models, and were adjusted for in the final regression models.

MRI Patterns of Brain Injury

The distribution of MRI patterns of brain injury among the study cohort is shown in the Figure.

Post-rewarming brain MRIs were interpreted as normal in 37/62 (60%) of infants with normal blood glucose values compared with 37/116 (32%) of infants with an abnormal

glucose profile (unadjusted $P<.001$, adjusted $P=.02$). Of the 151 infants with scored post-rewarming MRIs, the distribution of distinct MRI patterns of brain injury differed among the glycemic groups (unadjusted $P=.004$, adjusted $P=.03$, Figure, A).

Twenty-seven (15.2%) infants died prior to the brain MRI. Of these, 6 infants had normal blood glucose values, 3 developed hypoglycemia only, 12 developed hyperglycemia only, and 6 had episodes of both hypoglycemia and hyperglycemia within first 24 hours ($P=.30$). Including the infants who died prior to MRI, the distribution of distinct MRI patterns of brain injury differed among the glycemic groups (unadjusted $P=.009$), but not after adjusting for co-variates ($P=.09$) (Figure, B).

Infants with hypoglycemia had higher adjusted odds of WS or focal-multifocal strokes compared with infants with normal blood glucose values (aOR 6.0, 95% CI 1.5–24.2) (Table III). Infants with hyperglycemia had higher odds (unadjusted OR 3.3, 95% CI 1.2–8.9) of BG predominant or global injury compared with normoglycemic infants, but this relationship was not statistically significant after adjusting for covariates (aOR 1.9, 95% CI 0.6–5.6). Infants with labile glucose had higher adjusted odds of WS or focal-multifocal strokes (aOR 6.6; 95% CI 1.6–27.0) as well as predominant BG or global injury (aOR 5.6; 1.1–29.3).

Discussion

We report that early postnatal glycemic profiles are associated with distinct patterns of injury on brain MRI in infants with moderate-to-severe HIE who received therapeutic hypothermia. Infants with normal blood glucose values with HIE had the least severe multi-organ failure and brain injury on MRI. Infants with hypoglycemia had a predominant pattern of injury involving WS regions and focal/multifocal strokes. Infants with hyperglycemia had a higher likelihood of a predominant BG or global pattern of injury compared with infants with normal blood glucose values but not after adjusting for covariates. Infants with labile glucose had higher odds of both patterns of injury compared with infants with normal blood glucose values. These findings support the hypothesis that early postnatal glycemic profiles may help to identify distinct phenotypes and potentially provide early insight into the underlying pathophysiology of these HIE phenotypes.

Prior studies evaluating MRI injury patterns or glycemic profiles in infants with HIE have involved cohorts that were heterogeneous or were reported in the pre-cooling era. A strength of our study is the inclusion of a well-defined cohort of infants, all of whom received therapeutic hypothermia for HIE at a single center. We acknowledge the limitations of attempting to reconcile our study with previous reports, but we notice a consistent finding that infants with HIE who remain normoglycemic had the least MRI evidence of brain injury and the least multi-organ failure compared with infants who develop early glucose derangements.²⁷ A prior study reported that infants with hypoglycemia and HIE had higher rates of prenatal risk factors such as chorioamnionitis and chronic placental changes. Our observation that infants with hypoglycemia have higher odds of WS and focal-multifocal injuries is consistent with this, because these MRI patterns of injury have been classically attributed to prolonged and partial ischemic insults. This may explain the observed lack of

therapeutic response to hypothermia among hypoglycemic infants, as prolonged partial ischemia may represent pathogenesis of brain injury beyond the therapeutic window of hypothermia.

We speculate that early postnatal hyperglycemia may result from decreased glucose utilization by the metabolically depressed neonatal brain after a hypoxic-ischemic insult in the setting of intact gluconeogenesis and stress hormone responses. In previous reports infants with hyperglycemia were noted to have the highest rate of sentinel delivery complications and emergency cesarean deliveries suggesting a brief period of fetal hypoxia-ischemia close to time of birth and perhaps explaining their favorable response to hypothermia treatment. Our observation of an unadjusted association between hyperglycemia and predominant BG injury is consistent with this notion, as BG injury has been suggested to be the hallmark of acute profound asphyxia.⁷ However, that the relationship between hyperglycemia and brain injury pattern was not significant in our adjusted analyses suggests that its effects may be intertwined with level of encephalopathy. In addition to this complexity, it should be noted that infants with hyperglycemia had a higher frequency of normal MRI compared with the hypoglycemic group (Figure 1). Although predominant BG injury has been associated with worse neuromotor impairment compared with WS predominant injuries, the overall lower frequency of any MRI injury and perhaps better response to hypothermia among infants with hyperglycemia may explain their better long-term outcomes compared with infants with hypoglycemia reported previously.⁷

The observed higher odds of both WS or focal-multifocal injury as well as BG or global injury in infants with labile glucose may be multifactorial and further highlights the complex interplay between the initial insult, injury pathogenesis including response to treatment, and later neurodevelopmental outcome. We acknowledge that our attempt to identify distinct phenotypes of HIE based on a non-specific laboratory value may be simplistic and imprecise. Nonetheless, our study suggests that the clinical value of assessing early glycemic profile in HIE warrants further investigation. Identifying early, reliable methods to risk-stratify infants with HIE has important therapeutic implications. Therapeutic hypothermia provided during the first 6 hours after birth mediates its neuroprotective effect by multiple mechanisms and adjuvant agents like erythropoietin, xenon, melatonin, and others, also have distinct neurotrophic, anti-apoptotic, anti-inflammatory, and antioxidant mechanisms attributed to their proposed neuroprotective role.²⁸ It is likely that individualized treatment of infants with HIE with hypothermia plus specific adjuvant therapies directed towards distinct underlying pathophysiology may improve outcomes than with hypothermia alone. Our study findings indicate that glycemic profile may be helpful in providing insight into HIE pathogenesis, and that infants presenting with hypoglycemia during the first 24 hours of age may benefit from introduction of adjuvant therapies with a broader therapeutic window (eg, erythropoietin).

Limitations pertaining to any *post hoc* analysis should be considered when interpreting our study findings. Because all infants were born at outside hospitals and transferred to our neonatal intensive care unit, glucose concentrations during the first few hours prior to admission may not have been available or accurately documented for some patients. Sampling bias is possible due to multiple measurements in infants with risk factors for

developing hypoglycemia such as infants of diabetic mothers and those who were large or small for gestational age. These factors may have led to under-or overestimation of the true incidence of glucose derangements. However, the study is strengthened by the standard definition for inclusion criteria, protocol for obtaining blood tests, laboratory analysis, and managing glucose infusion rates and insulin administration at a single center. Our primary outcome of brain injury pattern on MRI could not be assessed in infants who died prior to MRI. Although infants who died presumably had the most severe brain injury, whether they had global or the severe spectrum of either BG or WS predominant injuries could not be ascertained. We secondarily analyzed the association of glycemic group with brain injury pattern including infants who died prior to MRI as a distinct category and found similar relationships, although our adjusted analyses were no longer significant. Our study lacks neurodevelopmental outcomes data as follow-up of these infants is ongoing. Keeping these limitations in mind, the hypotheses generated from our findings need to be verified with future prospective studies.

In this study, the early postnatal glycemic profile was associated with distinct patterns of brain injury on MRI. Infants with normal blood glucose values were most likely to have normal brain MRIs. Infants with hypoglycemia had a predominant WS pattern of injury or focal-multifocal strokes on brain MRI. Future studies are needed to investigate whether early glycemic profiles can provide an opportunity to individualize neuroprotective treatment to optimize outcomes in infants with HIE.

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Abbreviations:

aPTT	activated partial thromboplastin time
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
HCO₃	bicarbonate
95% CI	95% confidence interval
HIE	hypoxic ischemic encephalopathy

IQR	interquartile range
MRI	magnetic resonance imaging
OR	odds ratio
PT	prothrombin time

References

1. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum Dev* 2010 6;86:329–38. [PubMed: 20554402]
2. Hankins GD, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstet Gynecol* 2003 9;102:628–36. [PubMed: 12962954]
3. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. *N Engl J Med* 2012 5 31;366:2085–92. [PubMed: 22646631]
4. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013 1 31;1:CD003311.
5. Pappas A, Shankaran S, McDonald SA, Vohr BR, Hintz SR, Ehrenkranz RA, et al. Cognitive outcomes after neonatal encephalopathy. *Pediatrics* 2015 3;135:e624–34. [PubMed: 25713280]
6. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. *N Engl J Med* 2014 7 10;371:140–9. [PubMed: 25006720]
7. Inder TE, Volpe JJ. Mechanisms of perinatal brain injury. *Semin Neonatol* 2000 2;5:3–16. [PubMed: 10802746]
8. Jones MD, Jr, Burd LI, Makowski EL, Meschia G, Battaglia FC. Cerebral metabolism in sheep: a comparative study of the adult, the lamb, and the fetus. *Am J Physiol* 1975 7;229:235–9. [PubMed: 1147049]
9. Nadeem M, Murray DM, Boylan GB, Dempsey EM, Ryan CA. Early blood glucose profile and neurodevelopmental outcome at two years in neonatal hypoxic-ischaemic encephalopathy. *BMC Pediatr* 2011 2 4;11:10-2431-11-10.
10. Salhab WA, Wyckoff MH, Laptook AR, Perlman JM. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. *Pediatrics* 2004 8;114:361–6. [PubMed: 15286217]
11. Wong DS, Poskitt KJ, Chau V, Miller SP, Roland E, Hill A, et al. Brain injury patterns in hypoglycemia in neonatal encephalopathy. *AJNR Am J Neuroradiol* 2013 7;34:1456–61. [PubMed: 23436054]
12. Basu SK, Kaiser JR, Guffey D, Minard CG, Guillet R, Gunn AJ, et al. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. *Arch Dis Child Fetal Neonatal Ed* 2016 3;101:F149–55. [PubMed: 26283669]
13. Basu SK, Salemi JL, Gunn AJ, Kaiser JR, CoolCap Study Group. Hyperglycaemia in infants with hypoxic-ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study. *Arch Dis Child Fetal Neonatal Ed* 2017 7;102:F299–306. [PubMed: 27799322]
14. 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* 2005 2 19–25;365:663–70. [PubMed: 15721471]
15. de Vries LS, Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2010 5;95:F220–4. [PubMed: 20444814]
16. Gano D, Chau V, Poskitt KJ, Hill A, Roland E, Brant R, et al. Evolution of pattern of injury and quantitative MRI on days 1 and 3 in term newborns with hypoxic-ischemic encephalopathy. *Pediatr Res* 2013 7;74:82–7. [PubMed: 23618911]

17. van Kooij BJ, van Handel M, Nievelstein RA, Groenendaal F, Jongmans MJ, de Vries LS. Serial MRI and neurodevelopmental outcome in 9-to 10-year-old children with neonatal encephalopathy. *J Pediatr* 2010 8;157:221–7. [PubMed: 20381069]
18. Twomey E, Twomey A, Ryan S, Murphy J, Donoghue VB. MR imaging of term infants with hypoxic-ischaemic encephalopathy as a predictor of neurodevelopmental outcome and late MRI appearances. *Pediatr Radiol* 2010 9;40:1526–35. [PubMed: 20512322]
19. Barkovich AJ, Ali FA, Rowley HA, Bass N. Imaging patterns of neonatal hypoglycemia. *AJNR Am J Neuroradiol* 1998 3;19:523–8. [PubMed: 9541312]
20. Miller SP, Ramaswamy V, Michelson D, Barkovich AJ, Holshouser B, Wycliffe N, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr* 2005 4;146:453–60. [PubMed: 15812446]
21. Okerefor A, Allsop J, Counsell SJ, Fitzpatrick J, Azzopardi D, Rutherford MA, et al. Patterns of brain injury in neonates exposed to perinatal sentinel events. *Pediatrics* 2008 5;121:906–14. [PubMed: 18450893]
22. Wong DS, Poskitt KJ, Chau V, Miller SP, Roland E, Hill A, et al. Brain injury patterns in hypoglycemia in neonatal encephalopathy. *AJNR Am J Neuroradiol* 2013 7;34:1456–61. [PubMed: 23436054]
23. Shankaran S, Natarajan G, Chalak L, Pappas A, McDonald SA, Laptook AR. Hypothermia for neonatal hypoxic-ischemic encephalopathy: NICHD Neonatal Research Network contribution to the field. *Semin Perinatol* 2016 10;40:385–90. [PubMed: 27345952]
24. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch Neurol* 1976 10;33:696–705. [PubMed: 987769]
25. 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 Am J Neuroradiol* 1998 1;19:143–9. [PubMed: 9432172]
26. Li AM, Chau V, Poskitt KJ, Sargent MA, Lupton BA, Hill A, et al. White matter injury in term newborns with neonatal encephalopathy. *Pediatr Res* 2009 1;65:85–9. [PubMed: 18787422]
27. Harteman JC, Nikkels PG, Benders MJ, Kwee A, Groenendaal F, de Vries LS. Placental pathology in full-term infants with hypoxic-ischemic neonatal encephalopathy and association with magnetic resonance imaging pattern of brain injury. *J Pediatr* 2013 10;163:968–95. [PubMed: 23891350]
28. Miller SP, Ramaswamy V, Michelson D, Barkovich AJ, Holshouser B, Wycliffe N, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr* 2005 4;146:453–60. [PubMed: 15812446]
29. Martinez-Biarge M, Diez-Sebastian J, Wusthoff CJ, Mercuri E, Cowan FM. Antepartum and intrapartum factors preceding neonatal hypoxic-ischemic encephalopathy. *Pediatrics* 2013 10;132:e952–9. [PubMed: 24019409]
30. Cowan F, Rutherford M, Groenendaal F, Eken P, Mercuri E, Bydder GM, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003 3 1;361:736–42. [PubMed: 12620738]
31. Tam EW, Haeusslein LA, Bonifacio SL, Glass HC, Rogers EE, Jeremy RJ, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. *J Pediatr* 2012 7;161:88–93. [PubMed: 22306045]
32. Edwards AD, Yue X, Squier MV, Thoresen M, Cady EB, Penrice J, et al. Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia. *Biochem Biophys Res Commun* 1995 12 26;217:1193–9. [PubMed: 8554576]
33. Gunn AJ, Gunn TR. The ‘pharmacology’ of neuronal rescue with cerebral hypothermia. *Early Hum Dev* 1998 11;53:19–35. [PubMed: 10193924]
34. Kelen D, Robertson NJ. Experimental treatments for hypoxic ischaemic encephalopathy. *Early Hum Dev* 2010 6;86:369–77. [PubMed: 20570449]

**P* value adjusted for Apgar at 5 min and Sarnat stage

Figure 1.
Distribution of patterns of brain injury on MRI stratified by glycemic groups
a) Among infants with post-rewarming MRI: *P*value .004 (adjusted 0.03)*

b) Including infants who died prior to MRI: *P* value .009 (adjusted .09)*

Table 1.

Baseline infant and maternal characteristics according to glycemic profile

Characteristics n (%) unless otherwise stated	Available data (n)	All subjects	Normoglycemia	Hypoglycemia only	Hyperglycemia only	Labile glucose	P Value
Number of infants	178	178	62 (34.8)	17 (9.6)	76 (42.7)	23 (12.9)	
Infant characteristics							
Birth weight, g: mean $\pm$ SD	178	3,308 $\pm$ 659	3,232 $\pm$ 538	3,585 $\pm$ 1,060	3,289 $\pm$ 599	3,369 $\pm$ 753	.25
Gestational age, wks, mean $\pm$ SD	178	38.7 $\pm$ 1.7	38.5 $\pm$ 1.5	38.4 $\pm$ 1.5	39.1 $\pm$ 1.6	37.9 $\pm$ 2.3	.019
Female	178	82 (46.1)	29 (46.8)	6 (35.3)	38 (50)	9 (39.1)	.63
Race	178						.023
White		84 (47.2)	22 (35.5)	13 (76.5)	35 (46.1)	14 (60.9)	
African-American		82 (46.1)	37 (59.7)	4 (23.5)	34 (44.7)	7 (30.4)	
Others		12 (6.7)	3 (4.8)	0 (0)	7 (9.2)	2 (8.7)	
Maternal characteristics							
Maternal diabetes	178	23 (12.9)	7 (11.3)	5 (29.4)	4 (5.3)	7 (30.4)	.002
Pre-eclampsia	178	14 (7.9)	9 (14.5)	0 (0)	3 (3.9)	2 (8.7)	.08
Maternal fever	178	20 (11.2)	8 (12.9)	1 (5.9)	8 (10.5)	3 (13.0)	.86
Chorioamnionitis	178	19 (10.7)	5 (8.1)	0 (0)	10 (13.2)	4 (17.4)	.26
Perinatal sentinel events	178	135 (75.8)	48 (77.4)	14 (82.4)	55 (72.4)	18 (78.3)	.79
Vaginal delivery	178	60 (33.7)	26 (41.9)	5 (29.4)	24 (31.6)	5 (21.7)	.3
Emergency cesarean delivery	178	99 (55.6)	32 (51.6)	8 (47.1)	46 (60.5)	13 (56.5)	.73
Postnatal characteristics							
Apgar 1-min, median (IQR)	175	1 (1–2)	1.5 (1–3)	1.5 (0–2)	1 (1–2)	1 (0–3)	.24
Apgar 5-min, median (IQR)	175	4 (2–5)	4 (3–6)	3.5 (2–5)	3 (2–5)	3 (1–5)	.017
Apgar 10-min, median (IQR)	145	5 (3–7)	6 (4–7)	5 (4–7)	5 (3–6)	3 (0–6)	.002
Delivery room intubation	178	155 (87.1)	52 (83.9)	15 (88.2)	65 (85.5)	23 (100)	.24
Delivery room epinephrine	178	44 (25.7)	7 (11.9)	4 (25.0)	21 (28.8)	12 (52.2)	.001
Samat stage of encephalopathy	178						
Stage 3		41 (23.0)	7 (11.3)	3 (17.6)	24 (31.6)	7 (30.4)	.03
Stage 2		137 (77)	55 (88.7)	14 (82.4)	52 (68.4)	16 (69.6)	
Clinical seizure at presentation	178	46 (25.8)	12 (19.4)	7 (41.2)	22 (28.9)	5 (21.7)	.26
Electrographic seizure during cooling	160	55 (34.4)	17 (29.8)	4 (28.6)	25 (35.7)	9 (42.9)	.69

Characteristics n (%) unless otherwise stated	Available data (n)	All subjects	Normoglycemia	Hypoglycemia only	Hyperglycemia only	Labile glucose	P Value
Average 24 h glucose infusion rate	163	3.83 ± 1.3	3.89 ± 1.32	4.4 ± 1.78	3.65 ± 0.97	3.86 ± 1.92	.24
Insulin administration during cooling	178	33 (18.5)	2 (3.2)	0 (0)	24 (31.6)	7 (30.4)	<.001
Death prior to discharge	178	29 (16.3)	6 (9.7)	3 (17.6)	13 (17.1)	7 (30.4)	.19
Days of life when brain MRI performed	151	9 (7–11)	9 (7–10)	9 (7–11)	9 (7–11)	10 (8.5–13)	.19

Table II.

Metabolic and clinical measurements by glycemic profile

Metabolic parameter in first 24 hours of life	Overall		Normoglycemia		Hypoglycemia		Hyperglycemia		Labile Glucose		P Value
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD or Median (IQR)	n	Mean ± SD or Median (IQR)	n	Mean ± SD or Median (IQR)	
Glucose values range											
Minimum value (mg/dL)	178	67.3 ± 22.8	62	69.5 ± 12.4	17	32.5 ± 12.0	76	86.5 ± 37.6	23	35.8 ± 7.8	<.001
Maximum value (mg/dL)	178	201.6 ± 130.9	62	111.8± 20.3	17	115.7 ± 23.1	76	288.9 ± 135.4	23	263.0 ± 116.5	<.001
Acid-base parameters*											
p ^H	175	6.95 ± 0.20	60	6.98 ± 0.21	17	6.96 ± 0.16	75	6.95 ± 0.20	23	6.87 ± 0.19	.18
Base deficit	150	17.9 ± 7.6	54	18.0 ± 5.9	15	15.3 ± 11.4	61	18.6 ± 8.5	20	17.5 ± 4.9	.52
Hematologic parameters											
Lowest platelet in 72 h (10 ⁹ /L)	177	116 ± 55	62	131 ± 51	17	92 ± 42	75	119 ± 54	23	85 ± 65	.002
Liver and coagulation parameters											
Peak PT in 72 h (sec)	177	26.7 ± 9.9	62	24.5 ± 8.3	17	29.9 ± 13.2	75	26.2 ± 9.4	23	31.9 ± 10.5	.008
Peak aPTT in 72 h (sec)	173	57.0 ± 24.9	60	53.4 ± 23.2	16	55.4 ± 26.9	74	59.5 ± 27.3	23	59.5 ± 19.0	.52
Peak AST in 72 h (IU/L)	178	603 ± 1070	62	345 ± 634	17	556 ± 492	76	585 ± 1070	23	1396 ± 1781	<.001
Peak ALT in 72 h (IU/L)	178	214 ± 362	62	135 ± 231	17	259 ± 286	76	190 ± 324	23	477 ± 628	.001
Renal function											
Peak BUN in 72 h (mg/dL)	178	16.3 ± 7.0	62	15.7 ± 7.4	17	16.4 ± 6.5	76	16.2 ± 7.1	23	18.4 ± 6.1	.48
Peak creatinine in 72 h (mg/dL)	178	1.26 ± 0.5	62	1.17 ± 0.5	17	1.34 ± 0.3	76	1.26 ± 0.4	23	1.45 ± 0.6	.09

* Acid base parameters on first blood gas after admission to the site NICU

Table III.

Odds Ratios of MRI patterns of brain injury stratified by glycemic profile

Predominant Pattern of Injury	Hypoglycemia vs. Normoglycemia		Hyperglycemia vs. Normoglycemia		Labile Glucose vs. Normoglycemia		Hypoglycemia vs. Hyperglycemia	
	OR	Adjusted OR*	OR	Adjusted OR*	OR	Adjusted OR	OR	Adjusted OR
Watershed or Focal-Multifocal Infarcts	6.9 (1.8–26.6)	6.0 (1.5–24.2)	1.8 (0.7–4.4)	1.6 (0.7–4.1)	6.2 (1.6–24.2)	6.6 (1.6–27.0)	3.8 (1.0–14.4)	3.6 (0.9–14.3)
Basal ganglia or Global Injury	1.3 (0.1–13.7)	1.0 (0.1–11.6)	3.3 (1.2–8.9)	1.9 (0.6–5.6)	6.6 (1.4–30.9)	5.6 (1.1–29.3)	0.4 (0.0–3.9)	0.6 (0.1–5.9)
Died prior to MRI	4.6 (0.8–26.0)	3.2 (0.4–26.0)	2.6 (0.9–7.6)	0.8 (0.2–3.4)	9.3 (2.0–42.8)	5.0 (0.7–34.2)	1.8 (0.4–9.4)	3.8 (0.5–29.2)

* Adjusted OR (adjusted for Samat stage of encephalopathy Apgar score at 5 minutes)