Hyperglycemia and Glucose Variability Are Associated with Worse Brain Function and Seizures in Neonatal Encephalopathy: A Prospective Cohort Study

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Objectives To investigate how glucose abnormalities correlate with brain function on amplitude-integrated electroencephalography (aEEG) in infants with neonatal encephalopathy.

Study design Neonates born at full term with encephalopathy were enrolled within 6 hours of birth in a prospective cohort study at a pediatric academic referral hospital. Continuous interstitial glucose monitors and aEEG were placed soon after birth and continued for 3 days. Episodes of hypoglycemia (≤50 mg/dL; ≤2.8 mmol/L) and hyperglycemia (>144 mg/dL; >8.0 mmol/L) were identified. aEEG was classified in 6-hour epochs for 3 domains (background, sleep–wake cycling, electrographic seizures). Generalized estimating equations assessed the relationship of hypo- or hyperglycemia with aEEG findings, adjusting for clinical markers of hypoxia-ischemia (Apgar scores, umbilical artery pH, and base deficit).

Results Forty-five infants (gestational age 39.5 ± 1.4 weeks) were included (24 males). During aEEG monitoring, 16 episodes of hypoglycemia were detected (9 infants, median duration 77.5, maximum 220 minutes) and 18 episodes of hyperglycemia (13 infants, median duration 237.5, maximum 3125 minutes). Epochs of hypoglycemia were not associated with aEEG changes. Compared with epochs of normoglycemia, epochs of hyperglycemia were associated with worse aEEG background scores (B 1.120, 95% CI 0.501-1.738, $P < .001$), less sleep–wake cycling (B 0.587, 95% CI 0.417-0.757, $P < .001$) and more electrographic seizures (B 0.433, 95% CI 0.185-0.681, $P = .001$), after adjusting for hypoxia–ischemia severity.

Conclusions In neonates with encephalopathy, epochs of hyperglycemia were temporally associated with worse global brain function and seizures, even after we adjusted for hypoxia–ischemia severity. Whether hyperglycemia causes neuronal injury or is simply a marker of severe brain injury requires further study. *(J Pediatr 2019;209:23-32)*.

Hypoxic–ischemic encephalopathy (HIE) is the most common cause of neonatal encephalopathy and leads to significant mortality and morbidity.[1] Although therapeutic hypothermia has improved outcomes at 18 months of age,[2,3] mortality in moderate-to-severe HIE occurs in approximately 25% of infants, with major neurodevelopmental disability in approximately 20% of survivors.[3] Thus, current neuroprotective strategies require further optimization.

Both hypoglycemia and hyperglycemia are common in neonatal encephalopathy[4-6] and are potentially modifiable risk factors. In neonates with encephalopathy, hypoglycemia has been detected in 34%[4-6] and hyperglycemia in 50%[4] using intermittent glucose testing. Although studies suggest that hypoglycemia and hyperglycemia may be independently associated with worse outcomes in these neonates,[4,6-9] available evidence is conflicting and putative mechanisms remain poorly understood.[10-15] Furthermore, glucose instability and rapid correction of hypoglycemia also may be associated with worse outcomes.[16-18]

Despite the aforementioned observations, there is limited evidence available to guide effective hypoglycemia management to prevent associated brain injury and neurodevelopmental sequelae.[19] The Pediatric Endocrine Society advise that a "safe target" during the first 48 hours should be close to the mean for healthy newborns and above the threshold for neuroglycopenic symptoms (50 mg/dL;

aEEG	Amplitude-integrated electroencephalography
CGM	Continuous glucose monitor
HIE	Hypoxic–ischemic encephalopathy
MRI	Magnetic resonance imaging

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2.8 mmol/L).[20] Moreover, reference ranges in healthy term newborns may not be appropriate in infants at risk for impaired metabolic adaptation, as individual susceptibility to brain injury can vary depending on comorbid conditions and an infant's ability to produce and use alternative fuels.[21] To inform neuroprotective glucose-management strategies, we investigated how abnormalities in glucose homeostasis correlate with brain function on amplitude-integrated electroencephalography (aEEG) in the context of neonatal encephalopathy.

Methods

Infants were enrolled in an ongoing prospective cohort study of infants born full term with neonatal encephalopathy transferred to The Hospital for Sick Children. This report includes subjects enrolled from August 2014 to March 2017, a consecutive convenience sample of the Neurological Outcome of Glucose in Neonatal encephalopathy (NOGIN) study cohort. The institutional research ethics board approved the study protocol, and parents or guardians of all participating neonates provided written informed consent. Newborns with encephalopathy were eligible if they had abnormal consciousness with either neonatal seizures or abnormalities in tone or reflexes. Exclusion criteria included suspected or confirmed congenital malformations, inborn errors of metabolism, congenital infections, gestational age <36 weeks, weight <1500 g, or if it was expected that a continuous glucose monitor (CGM) could not be attached within 6 hours of life.

Clinical data were collected from patient medical records. All point-of-care testing and laboratory glucose measurements obtained clinically were collected. Point-of-care testing performed with i-STAT (Abbott Laboratories, Abbott Park, Illinois) uses the gold standard glucose oxidase reaction, and was thus considered as laboratory values for CGM calibration. Study data were stored and managed using research electronic data capture (REDCap, Vanderbilt University, Tennessee) hosted at The Hospital for Sick Children.[22]

Therapeutic hypothermia was initiated within 6 hours after birth if clinically indicated, with target temperature (33-34°C core temperature) continued for 72 hours followed by gradual rewarming by 0.5°C per hour over 6 hours. Low-dose morphine or fentanyl was provided during hypothermia as needed.

aEEG Monitoring and Analysis

aEEG was commenced as soon as possible after admission as part of routine clinical care and interpreted by the neonatology team. Subsequent research analysis of aEEG recordings was performed by a single neurologist blinded to clinical course, glucose levels, and neurologic outcome. Only dual-channel aEEG recordings (C3-P3, C4-P4) were included. Over 6-hour epochs, the aEEG background was graded on an ordinal scale: 0: continuous normal voltage (aEEG maximum >10 μV and minimum >5 μV); 1: discontinuous normal voltage (aEEG maximum >10 μV and minimum ≤5 μV); 2: burst suppression pattern (virtual absence of activity [<2 μV] between bursts of high voltage [>25 μV]); 3: continuous low-voltage (aEEG maximum ≤10 μV); and 4: flat trace (isoelectric activity, aEEG maximum ≤5 μV). The predominant, best, and worst background scores in each epoch were graded. Sleep–wake cycling was graded as: 0: developed cycling; 1: immature cycling; and 2: no cycling. Seizures were graded as: 0: no seizures; 1: single seizure; 2: repeated seizures (2 or more); and 3: status epilepticus ("saw-tooth pattern"), defined as continuous or recurrent seizures lasting at least 30 minutes, or for more than 50% of the recording time.[23-28]

Continuous Interstitial Glucose Monitoring

Medtronic iPro2 professional continuous glucose monitors with Enlite sensors (Medtronic of Canada Ltd, Brampton, Ontario) were placed as early as possible after study enrollment, either during transport or on admission to hospital. The sensors were inserted interstitially into the lateral aspect of the thigh and secured with clear adhesive dressing. In both infants born term and preterm, this device has been used safely over a 7-day period and shown to be well tolerated.[29,30] The iPro2 monitor is a blinded device that records average interstitial glucose concentrations every 5 minutes. These data were not made available to the care team due to limited evidence for treating newborns based on these measures. Clinicians treated newborns for hypoglycemia or hyperglycemia based on current standard of care using intermittent glucose testing. As per institutional protocol, blood glucose concentrations <49 mg/dL (2.7 mmol/L) were treated with intravenous dextrose, increasing glucose infusion rates or glucagon. Hyperglycemia was treated with insulin infusion as clinically indicated.

Continuous glucose monitoring was continued for 72 hours, after which the data were downloaded onto a Windows-based notebook computer running Medtronic software. Laboratory blood glucose values were used to calibrate the CGM. Due to software cut-offs, interstitial glucose readings <40 and >400 mg/dL (<2.2 and >22.2 mol/L) were recalculated manually using the interstitial signal values from the raw CGM data immediately before and after, using an equation provided by Medtronic.

For the study, hypoglycemia was defined as blood or interstitial glucose ≤50 mg/dL (2.8 mmol/L) and hyperglycemia as glucose >144 mg/dL (8.0 mmol/L). Episodes of interstitial glucose derangements were defined as 2 or more consecutive data points (≥10 minutes) outside the normal range. Episodes of glucose derangement were treated as contiguous if they were separated by brief periods of normoglycemia lasting ≤10 minutes.

For each subject, mean, minimum, and maximum glucose levels were calculated based on interstitial measurements obtained over each 6-hour epoch. The area under the curve was calculated as the area of interstitial glucose concentration over/under the normal glucose

range (hours*mg/dL), reflecting the extent and duration of the episode of interstitial glucose derangement. Glucose variability was quantified using the SD, coefficient of variation (SD/mean), and mean glucose rate of change per hour (mg/dL/h).

Statistical Analyses

All statistical analyses were computed using SPSS, version 20, software (IBM Corp, Armonk, New York). Demographic data were summarized using descriptive statistics. The primary analyses compared aEEG scores (background, sleep–wake cycling, and seizure scores) during 6-hour epochs containing episodes of hypoglycemia or hyperglycemia to normoglycemic epochs using generalized estimating equations for repeated measures with a linear scale response model. An independent correlation structure and robust variance estimators were used.

Generalized estimating equation has the advantage of providing robust SEs, whereas classical repeated-measures analysis is sensitive to misspecification of the correlation structure. Comparisons were made relative to normoglycemia because a previous study reported greater aEEG background discontinuity at plasma glucose concentrations both above or below 72 mg/dL (4 mmol/L).[31] Thus, hypo- or hyperglycemic epochs were compared with normoglycemic epochs within the same patient as well as the overall group. Findings were adjusted for clinical markers of hypoxia–ischemia severity: Apgar scores, umbilical artery pH, and base deficit. Secondary analyses investigated the association of the aEEG scores with other glucose measures (mean, maximum or minimum glucose values, duration of glucose disturbance, and area under the curve) and measures of glucose variability (SD, coefficient of variation, and mean glucose rate of change per hour). Two-tailed tests with P values of $< .05$ were considered statistically significant.

Results

Eighty families were approached to participate in the study. Of the 51 infants recruited (enrollment rate 64%), 6 were excluded (2 had no available interstitial glucose values, 3 had only single-channel [C3-C4] recordings, and 1 had no aEEG trace), leaving 45 eligible neonates. Demographic information is summarized in **Table I**. Compared with neonates who maintained normoglycemia on CGM, neonates with hypoglycemia on CGM had a greater mean gestational age and a greater mean umbilical artery pH. One patient was not cooled (did not meet institutional criteria for therapeutic hypothermia), and 4 patients died during the neonatal period.

Prevalence of Glucose Derangements

Overall, 37 infants (82%) demonstrated abnormal glucose values in the first 3 days including both interstitial values and blood glucose measurements obtained before insertion of the CGM. Thirteen neonates had hypoglycemia (29%), 16 neonates had hyperglycemia (36%), and 8 neonates had both hypo- and hyperglycemia (18%).

A mean of 55.6 hours (SD 20.4) of concurrent CGM and aEEG monitoring was available per infant. Thirty-four episodes of glucose derangements were captured on CGM concurrent with aEEG monitoring; 16 episodes of hypoglycemia in 9 infants (20%) and 18 episodes of hyperglycemia in 13 (29%). Hypoglycemic episodes had a median duration of 77.5 minutes (IQR 41.3-143.8) lasting up to 220 minutes. Hyperglycemic episodes had a median duration of 237.5 minutes (IQR 57.5-765) lasting up to 52.1 hours. During hypoglycemic episodes, the median interstitial glucose was 49 mg/dL (IQR 47-50, minimum 40 mg/dL), and during hyperglycemic episodes, the median glucose was 259 mg/dL (IQR 186-348, maximum 411 mg/dL).

Overall, 15 infants received treatment for hypoglycemia with intravenous dextrose boluses, including 1 infant who received 8 boluses with 10% dextrose and 1 with 12.5% dextrose. Furthermore, 1 infant had a glucose of 13 mg/dL [0.7 mmol/L] after 3 boluses of 10% dextrose and received a glucagon infusion. Only 3 episodes of hypoglycemia were treated during CGM, of which only 1 episode was treated during concurrent CGM and aEEG monitoring. Three infants received an insulin infusion for treatment of hyperglycemia during concurrent CGM and aEEG monitoring.

aEEG Measures During Epochs of Glucose Derangements

Six-hour epochs of aEEG containing episodes of hypoglycemia did not differ from normoglycemic aEEG epochs for any of the measures assessed (background score, sleep–wake cycling score, or seizure score). Compared with normoglycemic epochs, aEEG epochs containing hyperglycemia displayed worse aEEG background scores, less sleep–wake cycling and more frequent seizures, which remained significant after adjusting for clinical markers of HIE (**Figure** and **Table II**). In addition, these findings were still significant after adjusting for insulin treatment; aEEG epochs containing hyperglycemia still displayed worse aEEG background scores (B 1.211, 95% CI 0.659-1.763, $P < .001$), less sleep–wake cycling (0.368, 95% CI 0.092-0.644, $P = .009$), and more frequent seizures (B 0.347, 95% CI 0.070-0.624, $P = .014$). No seizures were recorded during epochs with hypoglycemia.

Other glucose measures were analyzed to quantify the severity of glucose derangements during each 6-hour epoch (**Table III**). Longer duration of hypoglycemia and greater area under the hypoglycemic curve were associated with worse aEEG background score, but no other measures were significant. Longer duration of hyperglycemia, greater maximum glucose values, and greater mean glucose values were associated with worse aEEG background, less sleep–wake cycling, and more frequent seizures. Greater area under the hyperglycemic curve was associated with worse aEEG background and less sleep–wake cycling.

The relationship of glucose variability with aEEG scores also was explored (**Table III**). After adjusting for clinical

markers of HIE, a greater SD in interstitial glucose concentration was associated with worse sleep–wake cycling and more frequent seizures, and greater coefficient of variation was associated with more frequent seizures. Faster rates of increase in glucose concentration were associated with worse sleep–wake cycling, but faster rates of decrease were not.

Discussion

Among infants with neonatal encephalopathy, epochs of hyperglycemia, but not hypoglycemia, were temporally associated with worse global brain function and greater seizure frequency on aEEG monitoring, even after we adjusted for clinical markers of HIE. Greater variability in glucose concentration also was associated temporally with worse sleep–wake cycling and more frequent seizures. These observations provide new insights into the dynamics of glucose homeostasis and brain function and highlight the potential importance of hyperglycemia on impaired brain function.

In this cohort of neonates with encephalopathy, epochs with hyperglycemia were significantly associated with worse aEEG background scores. These findings are consistent with previous studies in other age cohorts. In neonates born extremely preterm, moderate hyperglycemia was associated significantly with greater discontinuity on aEEG.[31] Another prospective study in neonates born premature found high blood glucose associated with depressed cerebral

Table I. Clinical and demographic data of the full study cohort, and subgroups of neonates with hypoglycemia and hyperglycemia, who were compared with those who maintained normoglycemia on continuous interstitial glucose monitoring

Characteristics	Full cohort N = 45	Normoglycemia N = 25	Hypoglycemia N = 7	*P* value	Hyperglycemia N = 11	*P* value
Sex	21 F:24 M	12 F:13 M	3 F:4 M	1.00	5 F: 6 M	1.00
Gestational age, wk, mean (SD)	39.5 (1.4)	39.2 (1.5)	40.5 (0.5)	**.001**	39.4 (1.2)	.75
Birth weight, g, mean (SD)	3414.4 (548.2)	3468.8 (670.0)	3413.3 (274.8)	.75	3337.1 (399.1)	.47
Birth length, cm, mean (SD)	50.1 (3.2)	50.6 (3.2)	49.4 (3.8)	.46	49.59 (3.1)	.37
Head circumference, cm, mean (SD)	34.2 (1.3)	34.3 (1.5)	34.1 (0.9)	.70	34.1 (1.3)	.73
Maternal diabetes, n (%)	5 (11)	4 (16)	0 (0)	.55	1 (9)	1.00
Type II diabetes mellitus	1 (2)	1 (4)	0 (0)		0 (0)	
Gestational diabetes	4 (9)	3 (12)	0 (0)		1 (9)	
Maternal hypertension, n (%)	4 (9)	3 (12)	0 (0)	1.00	1 (9)	1.00
Maternal preeclampsia/eclampsia	2 (5)	2 (8)	0 (0)		0 (0)	
Apgar score at 5 min, mean (SD)	4.2 (2.4)	3.7 (1.8)	5.4 (3.1)	.20	4.6 (2.5)	.32
Umbilical arterial cord pH, mean (SD)	6.99 (0.18)	6.96 (0.16)	7.17 (0.17)	**.03**	6.95 (0.20)	.92
Umbilical arterial cord BE, mean (SD)	–15.13 (6.79)	–15.83 (6.32)	–9.00 (7.43)	.08	–17.13 (6.83)	.65
Route of delivery, n (%)				.41		1.00
Vaginal	20 (44)	13 (52)	2 (29)		5 (45)	
Cesarean	25 (56)	12 (48)	5 (71)		6 (55)	
Sentinel event, n (%)*	17 (38)	9 (36)	2 (29)	1.00	5 (45)	.72
Hypoglycemia treatment, n (%)†	15 (33)		4 (57)			
IV dextrose	15 (33)		3 (43)			
Glucagon	1 (2)		1 (14)			
Hyperglycemia treatment, n (%)‡	3 (7)				3 (27)	
Insulin infusion						
Seizures, n (%)§	28 (62)	14 (56)	5 (71)	.67	7 (64)	.73
Clinical seizures only	16 (36)	9 (36)	5 (71)		1 (9)	
Electrographic and/or electroclinical seizures	12 (27)	5 (20)	0 (0)		6 (55)	
Antiepileptic medications, n (%)¶	26 (58)	12 (48)	5 (71)	.40	7 (63)	.48
Lorazepam only	6 (13)	3 (12)	2 (29)		0 (0)	
Phenobarbital	13 (29)	8 (32)	2 (29)		3 (27)	
≥2 AEDs	7 (16)	1 (4)	1 (14)		4 (36)	
Received opioids, n (%)	44 (98)	24 (96)	7 (100)	1.00	11 (100)	1.00
Minutes of concomitant aEEG and continuous glucose monitoring, mean (SD)	3256.9 (1280.0)	3135.6 (1263.5)	3401.4 (1264.7)	.63	3563.2 (1204.2)	.35

AED, antiepileptic drug; *BE*, base excess; *CGM*, continuous glucose monitoring; *F*, female; *IV*, intravenous; *M*, male.
Two subjects had both interstitial hypoglycemia and hyperglycemia events during concurrent aEEG monitoring.
Continuous variables were analyzed with the Student *t* test, whereas categorical variables were analyzed with the Fisher exact test.
Significant *P* values are shown in bold.
Hypoglycemia is defined as at least 2 interstitial glucose measurements ≤50 mg/dL and hyperglycemia is defined as at least 2 interstitial measurements >144 mg/dL.
*Sentinel hypoxic event (eg, cord prolapse, abruptio placentae) immediately before or during labor.
†Unit guidelines for treatment of hypoglycemia is to treat with an intravenous bolus of D10W 2 mL/kg if glucose is <49 mg/dL (2.7 mmol/L), followed by increasing glucose infusion rates or glucagon as needed. Note that treatment in hypoglycemia group refers to hypoglycemia treatments received while on CGM.
‡Unit guidelines for treatment of hyperglycemia is to first decrease the glucose infusion rate and to start an insulin infusion for blood glucose values repeatedly (on at least 2 occasions) >216 mg/dL (12 mmol/L). Note that treatment in hyperglycemia group refers to hyperglycemia treatments received while on CGM.
§Electrographic and/or electroclinical seizures were identified by clinical team on aEEG or continuous EEG. Clinical seizures only had no seizures captured on aEEG or continuous EEG monitoring.
¶Clinical and electrographic seizures were treated as per the Hospital for Sick Children guideline for management of neonatal seizures. The guidelines suggest initial treatment with lorazepam, followed by phenobarbital, levetiracetam, then a midazolam infusion as required for ongoing seizures.

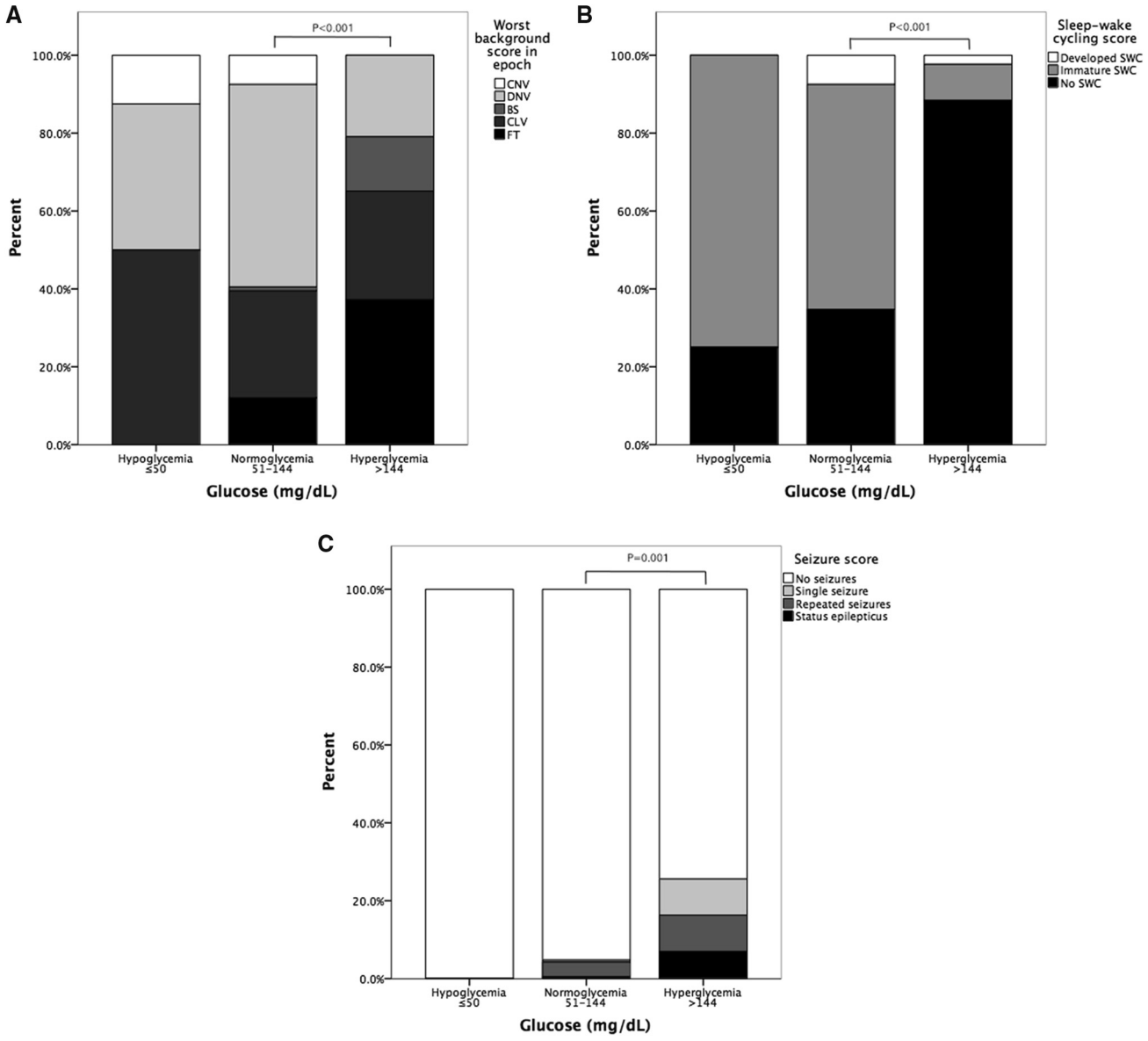

Figure. Bar graphs comparing aEEG scores with glucose derangement category during epochs of hypoglycemia, normoglycemia, or hyperglycemia. **A,** Worst background scores in epoch; **B,** sleep-cycling scores in epoch; and **C,** seizure scores in epoch. Scoring system for background: *BS*, burst-suppression; *CLV*, continuous low voltage; *CNV*, continuous normal voltage; *DNV*, discontinuous normal voltage; *FT*, flat tracing; *SWC*, sleep–wake cycling. Scoring system for SWC: developed SWC; Immature SWC; No SWC. Scoring system for seizures: no seizures; single seizure; repeated seizures; status epilepticus. SI conversion factor: to convert blood glucose concentration to millimoles per liter, multiply by 0.0555.

activity on aEEG.[32] Schumacher et al showed increased blood glucose in infants born premature was associated with decreased total absolute band power on continuous EEG monitoring during the first 3 days after birth.[33] A study using CGM and simultaneous continuous EEG monitoring in children with type 1 diabetes demonstrated that asymptomatic hyperglycemia was associated with changes in the power spectra of various EEG frequency bands.[34]

aEEG background abnormalities and their recovery are predictive of long-term neurodevelopmental outcome in neonates with HIE.[25,35-40] A meta-analysis of 8 studies before the advent of therapeutic hypothermia showed a pooled sensitivity of 91% and specificity of 88% of early severe aEEG tracings to predict poor neurodevelopmental outcome.[36] With therapeutic hypothermia, a persistently abnormal aEEG background at 48 hours remains an important prognostic indicator.[25,37,38]

In our cohort, hyperglycemia and greater glucose variability (as measured by SD and rate of glucose increase), also were associated with worse sleep–wake cycling scores. Neonatal sleep–wake cycling is a marker of brain function and enhances prediction of long-term outcomes in neonates

Table II. Association of glucose derangements with aEEG scores during 6-hour epochs containing hypoglycemia or hyperglycemia

Glucose derangements during epoch	Median (IQR)	Unadjusted regression slope (95% CI)	*P* value	Adjusted regression slope (95% CI)*	*P* value
Worst background score during epoch†					
Hypoglycemia	2 (1-3)	0.032 (−0.677 to 0.741)	.93	0.211 (−0.435 to 0.857)	.52
None	1 (1-3)				
Hyperglycemia	3 (2-4)	0.971 (0.324-1.618)	**.003**	1.120 (0.501-1.738)	**<.001**
Sleep cycling score during epoch†					
Hypoglycemia	1 (1-1.75)	−0.024 (−0.252 to 0.204)	.83	−0.020 (−0.226 to 0.186)	.85
None	1 (1-2)				
Hyperglycemia	2 (2-2)	0.586 (0.445-0.728)	**<.001**	0.587 (0.417-0.757)	**<.001**
Seizure score during epoch†					
Hypoglycemia	0 (0-0)	−0.095 (−0.176 to −0.013)	**.02**	−0.065 (−0.150 to 0.021)	.14
None	0 (0-0)				
Hyperglycemia	0 (0-1)	0.394 (0.170-0.617)	**.001**	0.433 (0.185-0.681)	**.001**

Significant *P* values are shown in bold.
Hypoglycemia is defined as at least 2 interstitial glucose measurements ≤50 mg/dL and hyperglycemia is defined as at least 2 interstitial measurements >144 mg/dL.
SI conversion factor: to convert blood glucose concentration to millimoles per liter, multiply by 0.0555.
*Adjusted for Apgar score, cord pH, and cord base excess.
†Reference category is normoglycemia.

with HIE.[25,41] A recent multimodality neuromonitoring study in neonates at risk for cerebral dysfunction showed that inefficient neonatal sleep patterns were independent predictors of 18-month neurodevelopmental outcome.[42]

We demonstrated that hyperglycemia and greater glucose dispersion (as measured by SD and coefficient of variation) were associated with seizure burden. There is growing evidence that greater seizure burden is associated with worse short- and long-term outcomes, adjusting for confounders including seizure etiology and illness severity.[43-48] Studies in neonates undergoing therapeutic hypothermia for HIE show a relationship between higher seizure burden and worse magnetic resonance imaging (MRI) injury scores in univariate[46,49-51] and multivariable analyses.[40,52]

There is increasing evidence of an association between hyperglycemia and neurodevelopmental outcomes in neonates born at term and preterm. Hyperglycemia is common in infants born preterm and has been associated with increased mortality, short-term morbidities,[53-56] and long-term outcomes, including white matter reduction on term-equivalent MRI scan[55] and neurologic and behavior problems at 2 years of age.[57] In a cohort of well babies at risk for hypoglycemia, greater glucose levels were associated with neurosensory impairment and cognitive delay at 2 years of age.[16] In infants with HIE, hyperglycemia has been shown to adversely affect long-term outcome in 2 small retrospective studies[7,8] and in a post-hoc analysis of the CoolCap therapeutic hypothermia trial in which both hypo- and hyperglycemia were common and associated with

Table III. Association of severity of glucose derangements and glucose variability with aEEG scores

	Worst background score during epoch		Cycling score during epoch		Seizure score during epoch	
Glucose measures during epoch	Adjusted regression slope (95% CI)*	*P* value	Adjusted regression slope (95% CI)*	*P* value	Adjusted regression slope (95% CI)*	*P* value
Hypoglycemia†						
Time hypoglycemic, h	0.299 (0.094-0.503)	**.004**	0.065 (−0.054 to 0.184)	.29	−0.023 (−0.059 to 0.013)	.21
Minimum glucose, mg/dL	0.006 (−0.007 to 0.018)	.39	0.005 (−0.0005 to 0.010)	.08	0.0005 (−0.002 to 0.002)	.96
Mean glucose, mg/dL	0.007 (−0.007 to 0.020)	.34	0.005 (−0.0003 to 0.011)	.06	0.001 (−0.001 to 0.003)	.42
Area under curve, h*mg/dL	0.069 (0.007-0.130)	**.03**	0.009 (−0.020 to 0.039)	.54	−0.008 (−0.019 to 0.003)	.16
Hyperglycemia†						
Time hyperglycemic, h	0.240 (0.102-0.380)	**.001**	0.128 (0.091-0.165)	**<.001**	0.072 (0.016-0.128)	**.01**
Maximum glucose, mg/dL	0.005 (0.001-0.009)	**.009**	0.003 (0.002-0.004)	**<.001**	0.001 (0.001-0.002)	**.001**
Mean glucose, mg/dL	0.005 (0.001-0.009)	**.006**	0.003 (0.002-0.004)	**<.001**	0.001 (0.0002-0.002)	**.02**
Area under curve, h*mg/dL	0.0009 (0.0001-0.002)	**.03**	0.006 (0.0003-0.001)	**<.001**	0.0001 (−0.00006 to 0.003)	.27
Glucose variability						
SD	0.029 (−0.003 to 0.060)	.08	0.021 (0.010-0.031)	**<.001**	0.023 (0.010-0.035)	**<.001**
Coefficient of variation, SD/mean	1.055 (−2.298 to 4.408)	.54	0.994 (−0.383 to 2.370)	.16	1.859 (0.183-3.536)	**.03**
Rate of glucose decrease, mg/dL/h	−0.017 (−0.072 to 0.038)	.54	−0.026 (−0.053 to 0.002)	.07	−0.009 (−0.025 to 0.006)	.25
Rate of glucose increase, mg/dL/h	0.021 (−0.034 to 0.076)	.46	0.020 (0.001-0.039)	**.04**	0.026 (−0.007 to 0.059)	.12

Significant *P* values are shown in bold.
Hypoglycemia is defined as at least 2 interstitial glucose measurements ≤50 mg/dL and hyperglycemia is defined as at least 2 interstitial measurements >144 mg/dL.
SI conversion factor: to convert blood glucose concentration to millimoles per liter, multiply by 0.0555.
*Adjusted for Apgar score, cord pH, and cord base excess.
†Reference category is normoglycemia.

unfavorable neurodevelopmental outcome by 18 months of age.[4] Longer duration of hyperglycemia and greater peak glucose levels also have been associated with mortality in the pediatric intensive care unit.[58] Episodes of hyperglycemia lasted longer than hypoglycemia in our cohort and the etiology is likely multifactorial. Hyperglycemia after hypoxia–ischemia may occur due to reduced net metabolism of severely damaged tissues[59] or prolonged elevation of stress hormones after asphyxia, which may be further prolonged by therapeutic hypothermia.[60] Importantly, studies have shown that tight glycemic control with insulin may be associated with adverse outcomes[61] and the appropriate threshold for treatment of hyperglycemia remains unclear. Furthermore, there are concerns for hypoglycemia with insulin infusions; thus, treating physicians have a greater threshold for intervention.

The relationship between glucose levels and brain injury is likely complex. A study in well infants demonstrated that less glucose stability and a steeper increase in glucose concentrations following hypoglycemia in the first 12 hours after birth were associated with neurosensory impairments at 2 years of age[16] and development of neurosensory impairment between 2 and 4.5 years of age.[18] Another retrospective cohort of infants with HIE born full term found that glucose variability was associated with severe neurodevelopmental disability.[17] An association between glucose variability and mortality likewise was shown in infants of very low birthweight born preterm,[62] infants born at term and children admitted to pediatric intensive care units,[63-65] and adults admitted to intensive care units.[66-69] Long-term outcomes are being assessed in our cohort to identify whether the acute aEEG changes associated with hyperglycemia and glucose variability are predictive of long-term neurodevelopmental outcomes.

In our primary analysis, we did not observe associations between hypoglycemia and brain function. This may be because episodes of hypoglycemia were generally shorter in duration (median 77.5 minutes) than hyperglycemic episodes (median 237.5 minutes). In our secondary analysis, longer duration of hypoglycemia and greater area under the hypoglycemic curve were associated with worse background scores, suggesting that the duration and severity of hypoglycemia may indeed be important. Neonatal hypoglycemia is associated with more severe neonatal encephalopathy,[70] and studies looking at long-term outcomes have shown hypoglycemia in infants with HIE to be associated with worse neurodevelopmental outcomes.[4,6,9] However, neonatal studies using aEEG have not been able to detect acute neurophysiological changes during hypoglycemia[71,72] except a case report of one critically ill neonate.[73] There are reports of children with recurrent hypoglycemia who demonstrated increased slow activity on conventional EEG with glucose concentrations ≤41 mg/dL (2.3 mmol/L), which improved with normalization of glucose concentrations.[74,75] In children with diabetes, an increase in low-frequency EEG activity was observed when glucose concentrations decreased ≤72 mg/dL (4 mmol/L).[76] Canine models of insulin-induced newborn hypoglycemia demonstrated progressive EEG slowing with declining glucose concentration[77] and suggest that the EEG response to hypoglycemia may depend not only on the concentration of glucose in the brain but also on the presence of associated metabolic derangements.[78] In HIE, a neonate's ability to produce and use alternative fuels may not be sufficient to compensate for low glucose levels, making them particularly vulnerable to hypoglycemia-induced brain injury.[21,71,79] Nonetheless, in our cohort we did not identify aEEG changes with hypoglycemia. The fact that we did not identify aEEG changes associated with hypoglycemia in our cohort suggests that either the impact of hypoglycemia on brain function is not immediately apparent on aEEG or our management protocols for hypoglycemia were adequate to maintain brain function in neonates with encephalopathy undergoing therapeutic hypothermia.

Our findings are consistent with a growing body of evidence that it is important to consider the potential harm of permissive hyperglycemia when trying to prevent hypoglycemia.[16,18,80] Several mechanisms have been proposed to explain the association of hyperglycemia with poor outcomes during critical illness, including dyslipidemia, inflammatory cytokine production, endothelial dysfunction, hypercoagulation,[81] and accelerated glucose toxicity leading to metabolic disturbances and increased cellular apoptosis.[81,82] The overproduction of superoxide by the mitochondrial electron-transport chain may underlie the mechanisms implicated in glucose-mediated vascular damage.[83] It also has been postulated that increased glucose variability would generate more reactive oxygen species due to hyperglycemia-induced oxidative stress.[84] Greater glucose variability has been associated with elevated markers of oxidative stress in adolescents.[85] Preclinical studies using cell culture and rodent models have shown that neuronal death was triggered by glucose reperfusion rather that hypoglycemia itself, and that hyperglycemia following hypoglycemia can worsen neuronal injury.[86,87] These findings suggest that the rate of correction of hypoglycemia as well as prevention of rebound hyperglycemia may be important.

Our study has several limitations. Because our study is observational, it does not establish a causal relationship between episodes of hyperglycemia and abnormal brain function. For example, it is possible that the observed association between hyperglycemia and aEEG scores remains confounded by HIE severity despite our attempts to adjust for this. Accounting for the clinical severity of HIE is challenging in this cohort because the clinical signs of hypoglycemia and HIE are overlapping. Furthermore, hypoglycemia in the setting of HIE may be associated with a more severe MRI pattern of perinatal hypoxia–ischemia in the corticospinal tracts[6] and initial clinical assessment of mild neonatal encephalopathy is frequently associated with MRI abnormalities.[88] Accordingly, we chose to adjust for Apgar scores, umbilical artery pH, and base deficit.

In this cohort of neonates with encephalopathy, hyperglycemia, but not hypoglycemia, was associated temporally with worse global brain function and seizures on aEEG than

normoglycemia. Glucose variability also was associated with seizures and impaired sleep–wake cycling. Although it remains to be determined whether these associations represent a causal link between hyperglycemia, glucose variability, and brain function and whether these immediate perturbations in brain function are associated with worse long-term outcomes, these findings are in keeping with growing evidence that hyperglycemia and glucose variability are associated with worse long-term neurodevelopmental outcomes.[4,6-9,16-18] Further studies are needed to clarify optimal treatment approaches for hypo- and hyperglycemia, in particular the optimal rate of glucose correction that maintains brain function, to prevent subsequent brain injury in this high-risk population. ■

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Data Statement

Data sharing statement available at www.jpeds.com

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