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Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy

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Abstract

Objective—To investigate the contribution of hypoglycemia in the first 24 hours after birth to brain injury in term newborns at risk for neonatal encephalopathy.

Study design—A prospective cohort of 94 term neonates born between 1994 and 2010 with early postnatal brain MRI studies were analyzed for regions of brain injury. Neurodevelopmental outcome was assessed at one year of age.

Results—Hypoglycemia (glucose <46mg/dL) in the first 24 hours after birth was detected in 16% of the cohort. Adjusting for potential confounders of early perinatal distress and need for resuscitation, neonatal hypoglycemia was associated with a 3.72-fold increased odds of corticospinal tract injury (P=0.047). Hypoglycemia was also associated with 4.82-fold increased odds of one-point worsened neuromotor score (P=0.038) and a 15-point lower cognitive and language score on the Bayley Scales of Infant Development (P=0.015).

Conclusion—Neonatal hypoglycemia is associated with additional risks in the setting of neonatal encephalopathy with increased corticospinal tract injury and adverse motor and cognitive outcomes.

Keywords

hypoglycemia; hypoxic-ischemic encephalopathy; neuroimaging; developmental outcome

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Neonatal encephalopathy occurs in 1–6 per 1000 live term births and is an important cause of mortality and long-term neurological disabilities, including cerebral palsy and cognitive impairment.[1] Current interventions are limited, including therapeutic hypothermia[2–5]. Therefore, avoiding secondary injury by maintaining homeostasis with attention to glucose, cardio-respiratory status and oxygenation is critical.[6] Although hypoxia-ischemia has been the major focus of research on neonatal encephalopathy, etiologies can be varied, including hypoglycemia and other metabolic derangements.

Independent of hypoxia-ischemia, hypoglycemia is a common problem in newborns. Neonatal hypoglycemia has been associated with adverse outcomes in term infants, resulting in visual impairment,[7] localization-related epilepsy,[8–10] and cognitive deficits.[11–13] Animal and human research suggest that the combination of perinatal hypoxia-ischemia and neonatal hypoglycemia may result in worse outcomes. In animal models, there is a higher risk of mortality and seizures when hypoglycemia occurs in the context of hypoxia-ischemia.[14, 15] In a cohort of newborns with severe acidemia, hypoglycemia was associated with higher rates of neonatal death and severity of encephalopathy.[16] In a case-control study of 60 neonatal encephalopathy cases and 60 term controls, there were significantly lower glucose levels in the cases, and a linear correlation between glucose level and severity of encephalopathy.[17] In a cohort of 52 term infants with encephalopathy, glucose <46 mg/dL in the first 6 hours after birth was associated with severe encephalopathy and adverse outcome at 2 years.[18]

Brain imaging in neonatal hypoglycemia is used to assess injury, and a correlation between hypoglycemia and parieto-occipital injury in isolated neonatal hypoglycemia has been identified.[7, 19, 20] However, no studies have systematically examined the patterns of brain injury associated with hypoglycemia in the context of neonatal encephalopathy. This study reports the relationship between early neonatal hypoglycemia, brain injury assessed by MRI, and neurodevelopmental outcome in a prospective cohort of term newborns at risk for encephalopathy.

METHODS

Term neonates born between 1994 and 2010 at the University of California San Francisco (UCSF) at risk for neonatal encephalopathy were included in this prospective cohort study. Inclusion criteria include an umbilical artery pH <7.1, umbilical artery base deficit >10, or a 5-minute Apgar score ≤5. Newborns were excluded if their gestational age at birth was <36 weeks or there were suspected or confirmed congenital malformations, inborn errors of metabolism, or congenital infections based on clinical examinations and laboratory studies. Newborns were also excluded if they were too unstable for transport to the MRI scanner or if death occurred before imaging was possible. Clinical data, including maternal, perinatal, and early postnatal history, were collected prospectively from patient charts. Neonatal hypoglycemia was defined as any clinical measurement of glucose <46 mg/dL (2.6 mmol/L) within the first 24 hours after birth.[18] Glucose measurements were obtained as deemed clinically necessary by the treating physicians. At risk infants were tested at 1, 2, 4, 6, 9, and 12 hours of age or more frequently if needed until blood glucose was stable >40 mg/dL. For glucose levels <40 mg/dL, either 5 mL/kg of D5W was fed to the asymptomatic infant or a bolus of 2–3mL/kg D10W given if the infant was symptomatic, and testing repeated after 20 minutes. An encephalopathy score, assessing mental status, ability to feed, need for respiratory support, tone, reflexes, and the presence of seizures was scored for the first 24 hours after birth.[21] Parental consent was obtained for all cases following a protocol approved by the Committee on Human Research at UCSF.

MRI studies

Neonates were transported to the MRI scanner in a custom MR-compatible incubator with specialized neonatal head coils to provide a quiet, well-monitored environment for the neonate, minimizing movement and improving signal-to-noise ratio. Scans were obtained at a median of 4 days after birth (intraquartile range 2–5 days). A series of standard MR sequences were performed for clinical assessment on all study subjects on a 1.5-T Signa EchoSpeed System (GE Healthcare, Milwaukee, WI) that include (1) T1-weighted sagittal and axial spin-echo images with repetition time (TR)/echo time (TE) of 500/11, 4-mm thickness, 1 excitation, 192×256 encoding matrix; and (2) T2-weighted axial dual echo, spin-echo with TR of 3 seconds, TE of 60 and 120 ms, 192×256 encoding matrix, 4-mm thickness. Diffusion-weighted imaging was performed using a spin-echo echo-planar imaging diffusion sequence with TE/TR 99/7000 ms, field of view 180 mm, 128×128, 3-mm slice thickness (no skip), b value of 700 s/m^2, six directions, and three averages; some infants had data obtained in 30 directions.

Brain injury patterns on MRI were identified by a pediatric neuroradiologist, blinded to the clinical course. All MRI sequences were used to assess for diffuse cortical brain, white matter, pericalcarine cortical, corticospinal tract, anterior cerebral intervascular boundary zone, posterior cerebral intervascular boundary zone, basal ganglia, thalamic, brainstem, or cerebellar injury. Corticospinal tract injury represents any injury in the perirolandic cortex or corticospinal tract through the brain and brainstem, including the posterior limb of the internal capsule, thereby capturing any injury to the full pathway of the upper motor neuron.

Neurodevelopmental outcome

Subjects were assessed in follow-up at 12 months of age to determine motor and cognitive outcomes. A standardized neurological examination was performed blinded and recorded by pediatric neurologists. Abnormalities were scored using the neuromotor score, a validated scoring system of motor outcome. The scores are denoted as follows: 0 - no neurological abnormalities; 1 - one abnormality in tone, deep tendon reflexes, or primitive reflexes; 2 - abnormalities in two of the three categories of tone, deep tendon reflexes, and primitive reflexes; 3 - decreased power; 4 - cranial nerve and motor involvement; 5 - spastic quadriplegia with cranial nerve involvement.[21, 22] A score of 3 or higher represents functional disability. Cognitive outcomes were assessed by a developmental psychologist (RJJ), blinded to the clinical course, using the Bayley Scales of Infant Development (Pearson, San Antonio, TX), a multi-scale battery used to identify deficits in young children, including the areas of cognitive, language, and motor domains. The 2nd edition (BSID-II) was used until 2007, when testing was switched to the 3rd edition (Bayley-III). Both editions are standardized and validated with a mean score of 100 and a standard deviation of 15 points. Children who were too disabled for cognitive testing were assigned a score of 50 for this study.

Statistical analysis

Statistical analysis was performed using Stata 11 (Stata Corporation, College Station, TX). Descriptive statistics were used to compare clinical features of subjects with and without hypoglycemia in the first 24 hours after birth. Due to possible confounding of the degree of perinatal hypoxia-ischemia on the association between hypoglycemia and outcome, regression analyses were performed adjusting for all available measures of severity of perinatal hypoxiaischemia, including umbilical artery pH, respiratory support (continuous positive airway pressure (CPAP) or intubation), cardiac massage, and 5-minute Apgar score. Adjustments were not made for 24-hour encephalopathy score or neonatal seizures, as these measures occur after and can be a result of neonatal hypoglycemia.[1] Logistic regression analysis was used to assess the association between neonatal hypoglycemia and regional

brain injury. Ordered logistic regression analysis was used to assess the association between neonatal hypoglycemia and neuromotor score. Linear regression analysis was used to assess the association between neonatal hypoglycemia and BSID-II mental developmental index (MDI) score. Due to possible differences in the editions, primary analysis was performed using only those subjects tested using the BSID-II. Secondary analysis considered a mean of the cognitive and language scores on the Bayley-III to be equivalent to the MDI score of the BSID-II, in order to consider all subjects.[23]

RESULTS

A total of 94 subjects were enrolled during the period of 1994 to 2010. Hypoglycemia was detected in the first 24 hours after birth in 15 of the 94 subjects (16%). The clinical demographics of this cohort separated into children with and without hypoglycemia detected in the first 24 hours after birth (Table I). Newborns with hypoglycemia demonstrated higher encephalopathy scores in the first 24 hours after birth and had a higher rate of neonatal seizures during the hospital course. Umbilical artery pH was also significantly lower in the newborns with hypoglycemia. Employment of therapeutic hypothermia in neonatal encephalopathy began at UCSF in 2008, affecting 11 subjects in this cohort. O infant had hypoglycemia in the first 24 hours after birth, and had normal neurologic examination and developmental testing at one year.

Brain injury patterns on MRI

Of the 94 subjects enrolled, 90 subjects had adequate brain MRI studies available for interpretation. Only one subject had the pattern of pericalcarine injury sometimes described with neonatal hypoglycemia, however no hypoglycemia was detected from clinical monitoring between birth and time of imaging.

Univariate logistic regression analyses were used to analyze the association between hypoglycemia in the first 24 hours after birth and brain injury patterns on MRI (Table II). The only brain structure found to be significantly associated with hypoglycemia was injury in the corticospinal tract. Multivariate logistic regression analysis adjusting for markers of perinatal hypoxia-ischemia resulted in a continued significant association between neonatal hypoglycemia and corticospinal tract injury (odds ratio 3.72, 95% CI 1.02 – 13.57, P=0.047).

Neurodevelopmental outcome

Out of the cohort of 94 subjects, one-year outcomes were available in 73 subjects. One subject died in the perinatal period, having experienced neonatal hypoglycemia (lowest glucose level was 17 mg/dL), seizures, and depressed neurological status. Thus, outcome data were available for 79% of this cohort.

Multivariate ordered logistic regression analysis was used to study the association between hypoglycemia and motor outcome. The median neuromotor score was 0 (intraquartile range 0–1) for subjects without and 1 (intraquartile range 0–3) for those with neonatal hypoglycemia. In univariate analysis, there was no significant association between hypoglycemia and worsening of the neuromotor score (odds ratio 2.85, 95% CI 0.85–9.48, P=0.089). Adjusting for markers of perinatal hypoxia-ischemia, hypoglycemia in the first 24 hours after birth was associated with a 4.82 times increased odds for a one point worsening of the neuromotor score at one year of age (95% CI 1.09 – 21.35, P=0.038). There were an inadequate number of subjects with therapeutic hypothermia to assess the associations to motor outcome in this cohort.

Considering only the 56 subjects tested with the BSID-II before 2007, the mean MDI score at 1 year was 92±13 for those without and 80±20 for those with neonatal hypoglycemia. Linear regression analysis was used to assess the association between hypoglycemia in the first 24 hours and cognitive outcome. In univariate analysis, hypoglycemia in the first 24 hours after birth was associated with 12-point lower MDI scores at one year of age (95% CI −23 – −1, P=0.027). Adjusting for markers of perinatal hypoxia-ischemia, hypoglycemia was associated with 15-point lower MDI scores (95% CI −26– −3, P=0.015). Further analysis was performed averaging the cognitive and language scores of the Bayley-III test to replace the MDI score, thereby including the 14 subjects who were tested since 2007. (Two children with normal neurological examinations did not receive cognitive testing, as well as the child who died in the perinatal period.) In univariate analysis, there was no significant association between hypoglycemia and MDI scores (-8, 95% CI −17 – 1, P=0.092). Again adjusting for potential confounders, hypoglycemia was associated with 12-point lower MDI scores (95% CI −23 – −2, P=0.02). There were an inadequate number of subjects with therapeutic hypothermia to assess the associations to cognitive outcome.

Corticospinal tract injury and outcome

The association between corticospinal tract injury on early MRI and 1 year motor and cognitive outcomes was further assessed. Corticospinal tract injury on MRI is associated with a 6.47-fold increased odds of one point increase in neuromotor score at 1 year (95% CI 2.18 to 19.22, P=0.001) or ordered logistic regression analysis. Corticospinal tract injury on MRI is not associated with BSID-II MDI scores (-6.83, 95% −15.82 to 2.15, P=0.13) or with the composite BSID-II and Bayley-III scores (-6.54, 95% CI −14.83 to 1.75, P=0.12) using linear regression analysis.

DISCUSSION

In this cohort study of MRI after neonatal encephalopathy, an independent association was found between hypoglycemia in the first 24 hours after birth and increased risk of injury to the corticospinal tract. The classic parieto-occipital pattern of brain injury after isolated neonatal hypoglycemia was not observed. In addition, associations were found between hypoglycemia in the first 24 hours after birth and motor and cognitive impairment at one-year follow-up.

Recent literature suggests a specific pattern of brain injury and long-term deficits after isolated neonatal hypoglycemia. Since first described by Spar et al in 1994 [24], isolated neonatal hypoglycemia has been associated with a posterior-predominant pattern of brain injury, as well as the underlying white matter tracts, corpus callosum, and thalamus.[19, 20] In a cohort of 35 term newborns with neonatal hypoglycemia without evidence for hypoxia-ischemia, the range of brain injury patterns were also extended to include white matter hemorrhage, basal ganglia, and the posterior limb of the internal capsule. (Of note, 11% of the cases of hypoglycemia in the cohort had cord pH 7.0–7.1, whereas all those with normoglycemia had cord pH >7.2.)[25] In the first six days after birth, diffusion-weighted imaging is the most sensitive for identification of this parieto-occipital brain injury[7], and later imaging may show gliosis and volume loss in the affected brain regions.[9] In keeping with this pattern of injury, long-term sequelae have been described in a neurologic syndrome of cortical visual loss, occipital localization-related epilepsy, and psychomotor retardation. [9, 10, 26]

Much more extensive literature exists regarding the pattern of brain injury and long-term outcome after perinatal hypoxia-ischemia. Two distinct patterns of brain injury have been described in term newborns. Prolonged mild to moderate hypoxia-ischemia has been associated with a pattern of injury that involves the watershed zones between the anterior

and middle cerebral artery and between the middle and posterior cerebral artery territories. Acute severe hypoxia-ischemia has been associated with a pattern of brain injury that involves the basal ganglia, thalamus, brainstem, sensorimotor cortex, and corticospinal tracts.[1, 27, 28]

Animal models suggested increased morbidity and mortality when perinatal hypoxiaischemia was combined with hypoglycemia, as compared with normoglycemic hypoxia-ischemia. Newborn rat pups subjected to anoxia who were normoglycemic survived ten-times longer than those with hypoglycemia.[14] When neonatal seizures occurred, ATP store depletion was much more significant in conjunction with hypoglycemia.[15] However, the implications of neonatal hypoglycemia in encephalopathy have been difficult to separate in humans. Higher rates of hypoglycemia were associated with more severe neonatal encephalopathy.[17] Hypoglycemia in the first six hours after birth was associated with worse two-year outcome after neonatal encephalopathy.[18]

Although different injury patterns are associated with isolated hypoglycemia and perinatal hypoxia-ischemia, our results suggest that a combination of the two conditions results in a pattern of more severe perinatal hypoxia-ischemia in the sensorimotor cortex and corticospinal tracts. The pattern of parieto-occipital brain injury described in isolated neonatal hypoglycemia is not seen, suggesting that this pattern may be seen predominantly in newborns without concomitant hypoxia-ischemia. Of note, because newborns who died before MRI could be performed were excluded from the study, this study may not capture the most severe spectrum of brain injury that may include those with neonatal hypoglycemia.

Many obstacles exist to understand the effects of hypoglycemia and perinatal hypoxia-ischemia on neonatal encephalopathy and long-term outcome. The first difficulty is our poor understanding of the degree and duration of hypoglycemia required to result in brain injury. Studies to date have used a range of cut-off values, the most common being 46mg/dL, as used in this study. Second, few independent markers exist to quantify the degree of perinatal hypoxia-ischemia. Often, the Sarnat and Sarnat method[29] to stage the progression of symptoms after perinatal hypoxia-ischemia has been used to inappropriately define the severity of hypoxia-ischemia. No reliable and specific laboratory markers exist to date, and thus the degree of perinatal hypoxia-ischemia is equated with the degree of clinical encephalopathy in the first few days after birth. Unfortunately, because hypoglycemia occurs early in life, the clinical signs of encephalopathy can also be a marker of injury associated with excessively low glucose.

This study uses early markers of neonatal distress, including 5-minute Apgar scores, umbilical artery pH, and the degree of respiratory and cardiac resuscitation to measure the degree of perinatal hypoxia-ischemia. Adjusting for these factors, neonatal hypoglycemia remains significantly associated with brain injury and adverse outcome. These findings seem to contradict Nadeem et al,[18] who found no association between hypoglycemia and injury after adjusting for the clinical severity of neonatal encephalopathy as determined using clinical signs in the first few days after birth. These current findings of worsened injury patterns of hypoxia-ischemia associated with hypoglycemia suggest that clinical severity of encephalopathy may not be specific to hypoxia-ischemia alone, but may also be a result of hypoglycemia. Encephalopathic newborns with hypoglycemia were also found to have higher degrees of encephalopathy in the first 24 hours after birth and an increased frequency of neonatal seizures as compared with normoglycemic newborns. Because one point can be given to the encephalopathy score in the presence of seizures, higher seizure frequency may partially explain the 2.5-point higher median encephalopathy scores in those neonates with hypoglycemia. This suggests that hypoglycemia may be associated with exacerbation of

encephalopathy. Analyses studying the effects of hypoglycemia that adjust for clinical severity of encephalopathy as a marker of hypoxia-ischemia may thus be inappropriate. Specific early markers of hypoxia-ischemia are required to accurately separate the effects of hypoxia-ischemia and hypoglycemia.

A limitation of this study is the lack of standardization of the frequency of measurement of glucose levels. Glucose levels in the first 24 hours were measured as clinically indicated and retrospectively reviewed, and thus may under-represent the true degree and frequency of hypoglycemia. Improved technologies to measure glucose in a continuous and noninvasive way will allow for better clarification of the degree and duration of hypoglycemia required for brain injury.

This study demonstrates that hypoglycemia is associated with a higher risk of corticospinal tract injury and adverse motor and cognitive outcomes at 12 months of age in infants with neonatal encephalopathy. A component of the cognitive deficits may reflect severe motor impairment limiting performance on cognitive testing. Relatively short follow-up reported in this study is a limitation for appreciating the full spectrum of neurodevelopmental deficits after hypoglycemia, and thus longer-term follow-up is ongoing to determine if these findings persist on subsequent follow-up examinations. This study also highlights the importance of finding specific early markers for adverse outcomes in neonatal encephalopathy, in order to better determine the specific effects of hypoxia-ischemia and concomitant factors such as hypoglycemia on brain injury and outcome.

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Table 1

Subject demographics separated by presence or absence of hypoglycemia (glucose <46mg/dL) documented within 24 hours after birth. Neonatal seizures includes both clinical and electrographically-confirmed seizures. Medians are compared using the K-sample equality of medians test. Means are compared using the t-test. Proportions are compared using the Fisher exact test.

	No hypoglycemia (n=79)	Hypoglycemia (n=15)	P-value
Gestational age (weeks, mean ± SD)	39.8 ± 1.4	39.6 ± 2.3	0.51
Birth weight (g, mean ± SD)	3303 ± 456	3274 ± 499	0.83
Male sex (n,%)	44 (56%)	10 (67%)	0.43
Umbilical artery pH (mean ± SD)	7.08 ± 0.14	6.98 ± 0.08	0.01
Meconium staining	38 (48%)	8 (53%)	0.72
Resuscitation with: **CPAP (n,%)** **Intubation (n,%)** **Cardiac massage (n,%)**	29 (37%) 37 (47%) 8 (10%)	7 (47%) 8 (53%) 1 (7%)	0.47 0.64 0.67
Apgar score at 5 minutes (median, IQR)	5 (4–7)	5 (4–6)	0.8
Encephalopathy score in first 24 hours (median, IQR)	2 (1–3)	4.5 (3–5)	0.007
Neonatal seizures (n,%)	13 (16%)	7 (47%)	0.009
Therapeutic hypothermia (n,%)	10 (13%)	1 (7%)	0.51

Table 2

Logistic regression of the association between neonatal hypoglycemia in the first 24 hours and injury to various brain structures on MRI. Univariate analyses demonstrate the unadjusted relationship between neonatal hypoglycemia and brain injury, while multivariate analyses adjust for markers of perinatal hypoxia-ischemia.

	Univariate analyses			Multivariate analyses		
Brain structure	**Odds ratio**	**95% CI**	**P-value**	**Odds ratio**	**95% CI**	**P-value**
Diffuse cortical	3.69	0.56 – 24.30	0.17	3.69	0.50 – 27.05	0.20
White matter	1.34	0.38 – 4.79	0.65	1.32	0.35 – 5.04	0.41
Corticospinal tract	3.50	1.05 – 11.66	0.04	3.72	1.02 – 13.57	0.047
Anterior watershed	1.96	0.62 – 6.25	0.25	2.05	0.61 – 6.91	0.24
Posterior watershed	1.42	0.45 – 4.44	0.55	1.72	0.51 – 5.80	0.38
Basal ganglia	2.11	0.66 – 6.74	0.21	2.22	0.65 – 7.66	0.20
Thalamus	2.46	0.76 – 7.93	0.13	2.77	0.79 – 9.68	0.11
Brainstem	2.61	0.22 – 30.75	0.45	5.32	0.29 – 98.50	0.26
Cerebellum	5.62	0.73 – 43.48	0.10	5.51	0.63 – 48.14	0.12