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Title: Neonatal hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonatal encephalopathy

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ABSTRACT

Objective: Hypoglycemia is a common occurrence in newborns, with higher incidence in those with neonatal encephalopathy. This study investigates the contribution of hypoglycemia in the first 24 hours of life 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 of life 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 3.5-fold increased odds of corticospinal tract injury (P=0.04). Hypoglycemia was also associated with 1.57-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.

INTRODUCTION

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 outcome 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 worsened outcomes. In animal models, a higher risk of mortality and seizures has been reported when hypoglycemia occurs in the context of hypoxia-ischemia.[14, 15] In a case-control study of 60 neonatal encephalopathy cases and 60 term controls, there were significantly lower glucose levels in the cases, and significant linear correlation between glucose level and severity of encephalopathy.[16] In a cohort of 52 term infants with encephalopathy, glucose <46 mg/dL in the first 6 hours of life was associated with severe encephalopathy and adverse outcome at 2 years.[17]

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, 18, 19] 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

Study subjects

Term neonates born between 1994 and 2010 at the University of California San Francisco (UCSF) with at risk for neonatal encephalopathy or a marker of perinatal depression were included in this prospective cohort study. Markers 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. Clinical data, including maternal, perinatal, and early postnatal history, was collected prospectively from patient charts. Neonatal hypoglycemia was defined as any clinical measurement of glucose <46 mg/dL within the first 24 hours of life.[17] 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 of life.[20] 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 of life (intraquartile range 2-5 days). A series of standard MR sequences were performed

for clinical assessment 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/m², six directions, and three averages; some infants had data obtained in 30 directions.

Clinical MRI reports were reviewed by a single pediatric neurologist (EWYT), and specific brain injury patterns were confirmed by a single pediatric neuroradiologist (AJB) 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.

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 and recorded by a pediatric neurologist. 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.[20,

21] Cognitive outcomes were assessed by a single developmental neuropsychologist (RJJ) using the Bayley Scales of Infant Development (BSID, 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-2) was used until 2007, when testing was switched to the 3rd edition (BSID-3). Both editions are standardized and validated with a mean score of 100 and a standard deviation of 15 points.

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 of life. 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 hypoxia-ischemia, including uterine 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. Ordinal 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 mental developmental index (MDI) score. Due to possible differences in the BSID editions, primary analysis was performed using only those subjects tested with the BSID-2. Secondary analysis considered a mean of the cognitive and language scores on the BSID-3 to be equivalent to the MDI score of the BSID-2, in order to consider all subjects.[22]

RESULTS

Study subjects

A total of 94 subjects matched our study criteria and were enrolled during the period of 1994 to 2010. Hypoglycemia was detected in the first 24 hours of life in 15 of the 94 subjects (16%). The clinical demographics of this cohort are described in Table 1, separated into children with and without hypoglycemia detected in the first 24 hours of life. Of interest, newborns with hypoglycemia demonstrated higher encephalopathy scores in the first 24 hours of life and had a higher rate of neonatal seizures during the hospital course. Uterine 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, of which only one was found to have hypoglycemia in the first 24 hours of life, showing normal neurological 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 displayed 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 of life and brain injury patterns on MRI. Results are summarized in Table 2. The only brain region 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 increased 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 ordinal logistic regression analysis was used to study the association between hypoglycemia and motor outcome. The mean neuromotor score was 1 ± 1 for subjects without and 2 ± 2 for those with neonatal hypoglycemia. In univariate analysis, there was a trend towards association between hypoglycemia and worsening of the neuromotor score (odds ratio 1.05, 95% CI -0.16 – 2.25, P=0.089). Adjusting for markers of perinatal hypoxia-ischemia, hypoglycemia in the first 24 hours of life was associated with a 1.57 times increased odds for a one point worsening of the neuromotor score at one year of age (95% CI 0.085 – 3.06, P=0.038). There were an inadequate number of subjects with therapeutic hypothermia to assess the associations to motor outcome in this cohort.

A change in protocol to test subjects using a newer version of the BSID test in 2007 complicated the analysis of cognitive outcome. Considering only the subjects tested with the BSID-2 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 of life 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 BSID-3 test to replace the MDI score. In univariate analysis, there is a trend towards an 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 in this cohort.

DISCUSSION

In this cohort study of MRI after neonatal encephalopathy, an independent association was found between hypoglycemia in the first 24 hours of life 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 this setting. In addition, associations were found between hypoglycemia in the first 24 hours of life and motor and cognitive impairment at one-year follow-up.

Recent literature has suggested a specific pattern of brain injury and long-term deficits after isolated neonatal hypoglycemia. The first description of brain injury after neonatal hypoglycemia was by Spar *et al.* in 1994, who reported a case of a newborn with over 15 hours of hypoglycemia.[23] An MRI of the child's brain at 19 days of age showed generalized thinning of the cerebral cortex, with a predominant pattern of injury in the parieto-occipital lobes. As this child had no other identified risk factors, the injury was attributed to hypoglycemia. Since then, other studies have confirmed this posterior-predominant pattern of brain injury, and additional involvement of the underlying white matter tracts, corpus callosum, and thalamus.[18, 19] In the first six days of life, diffusion-weighted imaging is the most sensitive for identification of this

parieto-occipital brain injury[7], while later imaging may show gliosis and volume loss in the affected brain regions.[9] In keeping with this pattern of injury, the long-term sequelae observed after isolated neonatal hypoglycemia have been described in a neurologic syndrome of cortical visual loss, occipital localization-related epilepsy, and psychomotor retardation.[9, 10, 24]

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 hypotension 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 hypotension has been associated with a pattern of brain injury that involves the basal ganglia, thalamus, brainstem, sensorimotor cortex, and corticospinal tracts.[1, 25, 26] The basal ganglia/thalamus pattern of injury has been associated with more severe neonatal signs including increased need for resuscitation and higher degree of encephalopathy, in addition to higher risks for adverse neurodevelopmental outcome at 30 months.[21, 27] Outcomes after perinatal hypoxia-ischemia include death in as many as 20% of affected infants and permanent impairments in motor and cognitive function in 25%.[28, 29]

Animal models have suggested increased morbidity and mortality when perinatal hypoxia-ischemia is combined with hypoglycemia, as compared with normoglycemic hypoxia-ischemia. Newborn rat pups subjected to anoxia who were normoglycemic were found to survive 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 have been associated with more severe neonatal

encephalopathy.[16] Hypoglycemia in the first six hours of life has also been found to be associated with worse two-year outcome after neonatal encephalopathy.[17]

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.

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. Secondly, few independent markers exist to quantify the degree of perinatal hypoxia-ischemia. Often, the Sarnat and Sarnat method[30] 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 of life. Unfortunately, since hypoglycemia occurs early in life, these clinical signs can also be a marker of injury associated with excessively low glucose.

This current study uses earlier markers of neonatal distress, including 5-minute Apgar scores, uterine 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.*,[17] who found no association of hypoglycemia and injury after adjusting for the clinical severity of neonatal encephalopathy as determined using clinical signs in the first few days of life. The 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 be augmented by hypoglycemia. Encephalopathic newborns with hypoglycemia were also found to have higher degrees of encephalopathy in the first 24 hours of life and an increased frequency of neonatal seizures as compared to normoglycemic newborns. Indeed, since one point can be given to the encephalopathy score in the presence of seizures, higher seizure frequency may partially explain the higher encephalopathy scores in those neonates with hypoglycemia. This observation suggests that hypoglycemia is associated with exacerbation of encephalopathy. Adjusting analyses for clinical severity of encephalopathy as a marker of hypoxia-ischemia may inappropriately also remove the effects of hypoglycemia. Specific early markers of hypoxia-ischemia are required to accurately separate the effects of hypoxia-ischemia and hypoglycemia.

Recently, therapeutic hypothermia has become standard of care for management of neonatal encephalopathy after multiple randomized trials showed decreased death and disability with treatment.[2-5] Specifically, therapeutic hypothermia has been associated with decreased risk of the basal ganglia/thalamus pattern of injury.[31, 32] It would be of great interest, therefore, to determine the effect of therapeutic hypothermia in the clinical situation of hypoglycemia and neonatal encephalopathy. However, there were inadequate numbers of such treated subjects in this cohort to analyze any associations.

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. Longer-term follow-up will be helpful 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 of life. 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)	39.84 ± 1.45	39.57 ± 2.27	0.51
Birth weight (g, mean ± SD)	3302.63 ± 456.18	3274 ± 498.53	0.83
Male gender (n,%)	44 (56%)	10 (67%)	0.43
Uterine 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,%)	29 (37%)	7 (47%)	0.47
Intubation (n,%)	37 (47%)	8 (53%)	0.64
Cardiac massage (n,%)	8 (10%)	1 (7%)	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 studying the association between neonatal hypoglycemia in the first 24 hours and injury in various brain regions on MRI. Univariate analyses demonstrate the unadjusted relationship between neonatal hypoglycemia and brain injury, while multivariate analyses adjust for markers of perinatal hypoxia-ischemia.

Brain region	Univariate analyses			Multivariate analyses		
	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