Hypoglycemia in Infants with Hypoxic-Ischemic Encephalopathy Is Associated with Additional Brain Injury and Worse Neurodevelopmental Outcome

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Objective To determine the incidence of hypoglycemia among infants with hypoxic-ischemic encephalopathy (HIE) who received therapeutic hypothermia, and to assess whether infants with hypoglycemia had more brain injury on magnetic resonance imaging (MRI) or differences in neurodevelopmental outcome.

Study design Single-center, retrospective cohort study including infants cooled for HIE. Hypoglycemia (blood glucose <36.0 mg/dL <2 hours and <46.8 mg/dL ≥2 hours after birth) was analyzed in the period before brain MRI. Brain injury was graded using a validated score. Motor and neurocognitive outcomes were assessed at 2 years for all survivors, and 5.5 years for a subset who had reached this age.

Results Of 223 infants analyzed, 79 (35.4%) had hypoglycemia. MRI was performed in 187 infants. Infants with hypoglycemia (n = 65) had higher brain injury scores (P = .018). After adjustment for HIE severity, hypoglycemia remained associated with higher injury scores (3.6 points higher; 95% CI, 0.8-6.4). Hyperglycemia did not affect MRI scores. In survivors at 2 years (n = 154) and 5.5 years (n = 102), a univariable analysis showed lower 2-year motor scores and lower motor and cognitive scores at preschool age in infants with hypoglycemia. After adjustment for HIE severity, infants with hypoglycemia had 9 points lower IQs (P = .023) and higher odds of adverse outcomes at preschool age (3.6; 95% CI, 1.4-9.0).

Conclusions More than one-third of infants cooled for HIE had hypoglycemia. These infants had a higher degree of brain injury on MRI and lower cognitive function at preschool age. Strategies to avoid hypoglycemia should be optimized in this setting. *(J Pediatr 2022;245:30-8)*.

Perinatal asphyxia followed by hypoxic-ischemic encephalopathy (HIE) is a major cause of neonatal mortality and long-term neurological sequelae in survivors.[1] Therapeutic hypothermia is currently standard of care, decreasing both mortality and morbidity.[1] More than 3 decades ago, Collins and Leonard described hyperinsulinism in the first hours after birth in infants with asphyxia, resulting in low blood glucose levels.[2] Furthermore, anaerobic glycolysis leads to a rapid depletion of glycogen stores.[2,3] Although the neonatal brain is able to cope with hypoglycemia by increasing cerebral blood flow and glucose extraction, decreasing cerebral energy requirements and enhancing the ability to use alternative sources, these mechanisms still fall short in the concomitant presence of asphyxia.[3] Prior studies have reported hypoglycemia rates up to 38.9% among infants with asphyxia with HIE receiving therapeutic hypothermia.[4-9] Both animal and neonatal studies have demonstrated a deleterious effect of hypoglycemia on the extent of brain injury in infants with asphyxia with HIE.[10,11] Lower glucose levels are associated with a higher degree of encephalopathy and worse neurodevelopmental outcome at 18-24 months of age.[4,5,11-14]

aEEG	Amplitude-integrated electroencephalography
Bayley-III-NL	Dutch version of the Bayley Scales of Infant and Toddler Development–Third Edition
GMDS	Griffiths Mental Development Scales
HIE	Hypoxic-ischemic encephalopathy
M-ABC-2-NL	Dutch version of the Movement Assessment Battery for Children–Second edition
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
PIQ	Performance IQ
WM/WS	White matter/watershed
WPPSI-III-NL	Dutch version of the Wechsler Preschool and Primary Scale of Intelligence–Third edition

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Magnetic resonance imaging (MRI) during the first week after birth is currently the standard imaging method in infants with HIE to assess the severity of brain injury and predict neurodevelopmental outcome.[15] The injury patterns of infants with HIE receiving therapeutic hypothermia have been well-studied; these infants also often show abnormalities of the mammillary bodies, and that mammillary body atrophy is strongly associated with episodic memory and neurocognitive outcomes at 10 years.[16,17] Few studies have described the MRI abnormalities of these infants taking the presence of hypoglycemia into account.[6] Furthermore, data on the long-term neurodevelopmental outcome of this group are limited.

The primary aim of the present study was to determine the incidence of hypoglycemia in infants with HIE who received therapeutic hypothermia and to assess whether infants with hypoglycemia had worse brain injury on early MRI. Secondary outcomes included neurodevelopmental outcomes at 2 and 5.5 years of age. We hypothesized that infants with asphyxia who received therapeutic hypothermia and also had hypoglycemia had more severe injury on early MRI, and subsequently worse neurodevelopmental outcomes at 2 and 5.5 years of age.

Methods

A single-center, retrospective cohort study was performed on infants with HIE after perinatal asphyxia born between February 2008 and February 2019 treated with therapeutic hypothermia at the level III neonatal intensive care unit (NICU) of our hospital. Data for some infants have been used previously.[16-24] The indications for therapeutic hypothermia have been described before and were not changed during the study period.[25] Infants with a postnatal collapse (sudden cardiovascular collapse after birth in infants initially considered healthy), congenital malformations, central nervous system infections, or genetic or metabolic disorders were excluded to explore the incidence of hypoglycemia. Subsequently, infants without an MRI were also excluded because we aimed to describe the MRI features and neurodevelopmental outcomes.

Blood Glucose

All glucose values before MRI were retrieved from the medical files. For those without an MRI, glucose values before death or discharge were analyzed. In most infants, glucose was measured in whole blood samples. Hypoglycemia was defined as glucose less than 36.0 mg/dL (<2.0 mmol/L) less than 2 hours and less than 46.8 mg/dL (<2.6 mmol/L) 2 or more hours after birth. Severe hypoglycemia was defined as glucose less than 28.8 mg/dL (<1.6 mmol/L) less than 2 hours and less than 36.0 mg/dL 2 or more hours after birth, in accordance with the intervention thresholds proposed by the Dutch guidelines based on studies by Alkalay et al and Adamkin et al.[26,27] Hyperglycemia was defined as glucose of more than 150 mg/dL (>8.3 mmol/L).[14] According to institutional protocol, infants who require resuscitation after birth and develop encephalopathy receive a continuous infusion of glucose 10% of 2-4 mg/kg/minute. Infants with asphyxia are screened for hypoglycemia at 1, 3, and 6 hours after birth and more frequently if needed. For glucose levels of less than 46.8 mg/dL combined with symptoms of hypoglycemia, an intravenous bolus of glucose 10% (2 mL/kg) is recommended, followed by continuous infusion of 6 mg/kg/minute glucose 10%. Asymptomatic infants who are less than 2 hours of age receive a continuous infusion of glucose 10% of at least 4 mg/kg/minute for a glucose of less than 28.8 mg/dL. Asymptomatic infants 2 hours of age or older recurrently having a glucose of less than 36.0 mg/dL or with a single glucose of less than 28.8 mg/dL receive continuous infusion of glucose 10% of at least 4 mg/kg/minute. In asymptomatic infants with a glucose of 21.6 mg/dL or less at 2 or more hours after birth a continuous infusion of 6 mg/kg/minute glucose 10% is started. For glucose levels of more than 144 mg/dL, decreasing the continuous glucose infusion is recommended. Insulin is not offered to term infants with asphyxia.

Neuroimaging

Brain MRI was performed preferably within the first week after birth on a 1.5 T or 3.0 T system (Philips). The standard MRI protocol included T1- and T2-weighted imaging, diffusion-weighted imaging including apparent diffusion coefficient mapping, susceptibility-weighted imaging, magnetic resonance venography, and proton magnetic resonance spectroscopy of the basal ganglia and thalamus using a TE of 144 or 288 ms. A comprehensive MRI score as described by Weeke et al was used to assess brain injury.[19] Abnormalities on magnetic resonance spectroscopy were analyzed using cut-offs for decreased N-acetylaspartate and increased lactate as described previously.[28] In addition, injury to the mammillary bodies was scored.[26] Brain injury was grouped into the following categories based on the predominant pattern of injury: normal, mild white matter/watershed (WM/WS), moderate-severe WM/WS, mild basal ganglia and thalamus injury, moderate-severe basal ganglia and thalamus injury, near-total injury (moderate or severe injury in both the deep gray matter and white matter/cortex), and stroke.[29]

Secondary Outcomes

Neurodevelopmental outcome was assessed at 24 months using the Dutch version of the Bayley Scales of Infant and Toddler Development–Third Edition (Bayley-III-NL) and at 5.5 years of age using the Dutch version of the Movement Assessment Battery for Children–Second edition (M-ABC-2-NL) and the Wechsler Preschool and Primary Scale of Intelligence–Third edition (WPPSI-III-NL).[30-32] For children who did not attend follow-up at 24 months, neurodevelopmental outcome assessed at 18 months using the Griffiths Mental Development Scales (GMDS) was used.[33] An adverse outcome was defined as death, severe hearing or visual impairment, cerebral palsy, or neurodevelopmental delay (GMDS developmental quotient <88, Bayley-III-NL motor

or cognitive composite score ≤85, M-ABC-2-NL ≤5th percentile, and/or WPPSI-III-NL total IQ, verbal IQ, performance IQ [PIQ], or a processing speed of ≤85).

Ethics

The Ethical Review Board of the University Medical Center Utrecht waived the requirement for informed consent for this study with pseudonymized clinical data.

Statistical Analyses

Data were analyzed using IBM SPSS 24. A univariable analysis was performed with Pearson χ^2 or Fisher exact tests to compare categorical variables, and the Mann-Whitney *U* tests to compare ordinal and continuous variables between infants with and without hypoglycemia. To assess the association of the severity of HIE, hypoglycemia, and hyperglycemia with primary and secondary outcomes, multivariable analysis including amplitude-integrated electroencephalography (aEEG) background pattern on admission scored according to the Hellström-Westas classification system, hypoglycemia, hyperglycemia, and the interaction between hypoglycemia and hyperglycemia was performed using linear regression for continuous outcomes (MRI score, cognitive, and motor function at 2 and 5.5 years of age) and logistic regression for binary outcomes (adverse outcome at 2 and 5.5 years of age).[34]

Results

Incidence of Hypoglycemia

During the study period, 255 infants were cooled. After exclusion of infants with a metabolic disorder (n = 2), congenital malformation or genetic disorder (n = 16), postnatal collapse (n = 13), and meningitis (n = 1), 223 were analyzed for 1 or more episodes of hypoglycemia (**Figure**; available at www.jpeds.com): 79 (35.4%) had hypoglycemia, which was severe in 50 (22.4%). Thirty-three (14.8%) had hypoglycemia within 6 hours after birth in the level II hospital. In 72 (91.1%) of the infants with hypoglycemia, the first episode occurred within 24 hours after birth. A total of 171 infants (76.7%) had hyperglycemia, of whom 58 (26.0%) in the level II hospital and 156 (70%) occurring less than 24 hours after birth. Sixty-four infants (28.7%) had both hyperglycemia and hypoglycemia. In 50 of these infants (78.1%), the first episode of hyperglycemia occurred after the episode of hypoglycemia. Thirty-five infants (hypoglycemia n = 14) died before MRI could be obtained. One infant in the nonhypoglycemic group was transferred to another hospital before an MRI could be performed. After exclusion of these infants, 187 infants were further analyzed. The baseline characteristics of these infants are presented in **Table I**. In the hypoglycemia group (n = 65, 34.8%) maternal hypertension during pregnancy was more common (13.8% vs 3.3%; $P = .013$) and lactate levels on admission were higher (median, 15 [IQR, 11] vs 13 [IQR, 9], $P = .014$). One mother with hypertension used labetalol, and the others received methyldopa, magnesium sulfate, or no medication. Fifteen infants (23.1% of the hypoglycemia group) had recurrent hypoglycemia, and in 2 (3.1% of the hypoglycemia group) hypoglycemia lasted more than 3 hours. The rate of infants with hyperglycemia was comparable between the hypoglycemia group and the nonhypoglycemic group (n = 52 [80.0%] and n = 91 [74.6%], respectively; $P = .406$). A comparable rate of infants died before discharge (hypoglycemia, n = 12 [18.5%] vs nonhypoglycemia n = 21 [17.2%]; $P = .831$). The baseline characteristics of survivors were comparable, except for higher lactate levels on admission ($P = .049$) and maternal hypertension being more common ($P = .044$) in the hypoglycemia group.

Univariable Analysis

Neuroimaging. Univariable analysis of MRI findings and the locations of brain injury are presented in **Table II**. Infants with hypoglycemia had a higher degree of brain injury according to the Weeke score ($P = .018$) and according to the predominant pattern of injury ($P = .034$). The most common patterns of injury among the hypoglycemia group were mild WM/WS (18.5%), moderate-severe WM/WS (15.4%), and near total injury (15.4%). Abnormalities of the mammillary bodies were present in 41.5% of infants with hypoglycemia.

Neurodevelopmental Outcomes. At 2 years, univariable analysis demonstrated comparable Bayley-III-NL cognitive composite scores (**Table III**). Motor scores were within the normal range, but significantly lower in the hypoglycemia group ($P = .028$). For 18 infants without a Bayley-III-NL, the motor and cognitive scores on the GMDS were analyzed. Comparable rates of adverse outcomes at 2 years of age were demonstrated in the hypoglycemia and nonhypoglycemic group. At analysis, 102 survivors (hypoglycemia n = 34; no hypoglycemia n = 68) had reached the age of 5.5 years. In this subgroup, lactate levels on admission were higher in the hypoglycemia group ($P = .008$). Other baseline characteristics were comparable. A WPPSI-III-NL was performed in 83 survivors (81.4%). In 1 infant a Snijders-Oomen nonverbal intelligence test was used instead of a WPPSI-III-NL to assess the total IQ.[35] One infant was tested in another center, but scores were unavailable for review. The remaining infants were not tested because of severe cerebral palsy (n = 2) or because parents declined testing (n = 15). In a univariable analysis, M-ABC-2-NL scores and WPPSI-III-NL total IQ, PIQ, and processing speed were significantly lower, and adverse outcomes at 5.5 years of age were more common among the survivors with hypoglycemia (**Table III**). Among the infants with hypoglycemia, the verbal IQ scores were significantly lower in those with abnormal mammillary bodies (median, 89 [IQR, 27] vs 100 [IQR, 34]; $P = .044$). The M-ABC-2-NL scores and WPPSI-III-NL total IQ, PIQ, and processing speed were comparable with those with normal mammillary bodies.

Table I. Baseline patient characteristics by blood glucose status (n = 187)

	Hypoglycemia (n = 65)		No hypoglycemia (n = 122)		
	Available for N (%)	Median (IQR) or N (%)	Available for N (%)	Median (IQR) or N (%)	*P* value
Maternal disease, n (%)	65 (100)		122 (100)		
Diabetes		2 (3.1)		7 (5.7)	.500
Hypertension/pre-eclampsia/eclampsia		9 (13.8)		4 (3.3)	**.013**
Fever during labor		6 (9.2)		4 (3.3)	.098
Premature rupture of membranes		10 (8.2)		2 (3.1)	.222
Perinatal sentinel event,* n (%)	65 (100)	34 (52.3)	122 (100)	71 (58.2)	.440
Mode of delivery, n (%)	65 (100)		122 (100)		.430
Spontaneous vaginal		15 (23.1)		36 (29.5)	
Assisted vaginal		10 (15.4)		23 (18.9)	
Emergency cesaraan		40 (61.5)		63 (51.6)	
Sex, male, n (%)	65 (100)	41 (63.1)	122 (100)	63 (51.6)	.134
Gestational age (weeks), median (IQR)	65 (100)	40.0 (1.86)	122 (100)	40.0 (2.79)	.610
Birth weight (grams), median (IQR)	65 (100)	3480 (880)	122 (100)	3500 (774)	.313
Birth weight Z-score, median (IQR)	65 (100)	−0.26 (1.69)	122 (100)	−0.21 (1.76)	.607
Apgar 1 minute, median (IQR)	64 (98.4)	2 (2)	122 (100)	1 (1)	.175
Apgar 5 minutes, median (IQR)	64 (98.4)	4 (3)	120 (98.3)	3 (2)	.288
pH umbilical artery, median (IQR)	57 (87.7)	6.93 (0.21)	103 (84.4)	6.89 (0.23)	.592
Lactate level on admission (mmol/L), median (IQR)	65 (100)	15 (11)	122 (100)	13 (9)	**.014**
Hyperglycemia before MRI, n (%)	65 (100)	52 (80.0)	122 (100)	91 (74.6)	.406
Sarnat stage, n (%)	61 (93.8)		118 (96.7)		.237
Stage I		10 (15.4)		34 (27.9)	
Stage II		42 (64.6)		65 (53.3)	
Stage III		9 (13.8)		19 (15.6)	
Thompson score on admission, median (IQR)	60 (92.3)	9 (4)	112 (91.8)	10 (5)	.653
aEEG BGP at start of hypothermia, n (%)	65 (100)		118 (96.7)		.552
CNV		0 (0)		3 (2.5)	
DNV		30 (46.2)		61 (50.0)	
BS		27 (41.5)		34 (27.9)	
CLV		5 (7.7)		4 (3.3)	
FT		3 (4.6)		16 (13.1)	
Use of AEDs, n (%)	65 (100)		122 (100)		.405
None		30 (46.2)		57 (46.7)	
1		16 (24.6)		39 (32.0)	
2		6 (9.2)		16 (13.1)	
≥3		13 (20.0)		10 (8.2)	
Death before discharge, n (%)	65 (100)	12 (18.5)	122 (100)	21 (17.2)	.831

BGP, background pattern; *BS*, burst suppression; *CLV*, continuous low voltage; *CNV*, continuous normal voltage; *DNV*, discontinuous normal voltage; *AED*, anti-epileptic drugs; *FT*, flat trace. Significant *P* values are set in bold.

*Defined as umbilical cord problem, placental problem (abruption, infarction, lesion, vasa previa), uterine rupture, macrosomia, shoulder dystocia, severe fetomaternal transfusion, other (eg, maternal hypotension during labor, difficult breech delivery).

Severe Hypoglycemia. Hypoglycemia was severe in 43 of the 187 infants (23.0%). Birth delivery by emergency cesarean was more common among these infants than among those with moderate hypoglycemia (74% vs 36%; $P = .003$). Other baseline characteristics were comparable. Infants with severe hypoglycemia had worse PIQ scores at preschool age than infants with moderate hypoglycemia (median, 95 [IQR, 24] vs median, 108 [IQR, 19], $P = .005$). Brain injury scores, the rate of adverse outcomes, motor scores, and other cognitive scores at 2 and 5.5 years did not significantly differ between the infants with moderate and severe hypoglycemia.

Multivariable Analysis

Results of the association between hypoglycemia or hyperglycemia with primary and secondary outcomes adjusted for the severity of HIE, expressed as aEEG background pattern on admission, are presented in Table IV. Hyperglycemia was not independently associated with MRI injury scores and outcome at 2 or 5.5 years of age. Hypoglycemia remained significantly associated with higher MRI brain injury scores on early MRI ($P = .011$) and lower WPPSI-III-NL total IQ scores at preschool age ($P = .023$). The odds of an adverse neurodevelopmental outcome at 5.5 years of age were 3.5 for survivors who had hypoglycemia (95% CI, 1.3-9.2). In a multivariable model including aEEG background pattern on admission, hypoglycemia, hyperglycemia, and the interaction between hypoglycemia and hyperglycemia, only an aEEG background pattern and hypoglycemia were significantly associated with outcome. With regard to secondary outcomes, a multivariable analysis demonstrated that infants with both hypoglycemia and hyperglycemia had slightly lower Bayley-III-NL cognitive composite scores owing to the interaction of hypoglycemia and hyperglycemia after adjustment for of HIE severity. The presence of hyperglycemia, and the interaction of hypoglycemia and hyperglycemia, were both not associated with motor scores at 2 and 5.5 years of age, WPPSI total IQ scores, or adverse outcomes at 2 and 5.5 years of age.

Discussion

This study demonstrated that 35.4% of infants with HIE who received therapeutic hypothermia at our NICU had

Table II. Initial brain MRI results

	Hypoglycemia (n = 65)	No hypoglycemia (n = 122)	*P* value
Brain injury differences			
Median age at MRI performance in days (IQR)	6 (2)	6 (2)	.454
Predominant pattern of injury, n (%)			**.034**
Normal	17 (26.2)	42 (34.4)	
Miscellaneous	2 (3.1)	8 (6.6)	
Mild WM/WS	12 (18.5)	35 (28.7)	
Stroke	2 (3.1)	2 (1.6)	
Moderate-severe WM/WS	10 (15.4)*	7 (5.7)	
Mild basal ganglia and thalamus	7 (10.8)	2 (1.6)	
Moderate-severe basal ganglia and thalamus	5 (7.7)	16 (13.1)	
Near total injury	10 (15.4)	10 (8.2)	
Total score (Weeke et al[18]), median (IQR)	8 (16)	4 (7)	**.018**
Total score including ^{1}H-MRS, median (IQR)	8 (19)†	4 (9)‡	**.023**
Locations of injury			
Grey matter subscore, median (IQR)			
Not including ^{1}H-MRS	0 (9)	0 (3)	
Including ^{1}H-MRS	2 (11)†	0 (5)‡	
White matter/cortex subscore, median (IQR)	4 (9)	3 (6)	
Additional injury, n (%)			
Cerebellum abnormal SI or diffusion restriction	15 (23.1)	16 (13.1)	
Cerebellar hemorrhage	4 (6.2)	4 (3.3)	
IVH	7 (10.8)	13 (10.7)	
SDH	16 (24.6)	33 (27.0)	
Sinovenous thrombosis	1 (1.5)	0 (0)	
Abnormalities on ^{1}H-MRS, n (%)			
Elevated lactate	23 (37.7)†	29 (23.8)‡	
Reduced N-acetylaspartate	25 (41.0)†	34 (27.9)‡	
Other abnormalities			
Abnormal mammillary bodies, n (%)§	27 (41.5)¶	37 (30.3)**	

CVST, cerebral venous sinus thrombosis; *^{1}H-MRS*, proton magnetic resonance spectroscopy; *IVH*, intraventricular hemorrhage; *SDH*, subdural hemorrhage; *SI*, signal intensity.
Differences in the severity of brain injury between the hypoglycemia group and nonhypoglycemic group are presented in the upper part of the table. Locations of brain injury are presented in the lower rows.
Significant *P* values are set in bold.
*One infant had both moderate-severe WM/WS predominant pattern of injury and stroke and was analyzed as having WM/WS predominant pattern of injury.
†Data available for 61 infants.
‡Data available for 116 infants.
§Defined as an increased signal T2 sequence with swelling or atrophy.
¶Data available for 64 infants.
**Data available for 121 infants.

hypoglycemia, which was severe in 22.4%. In more than 40% of infants with hypoglycemia, the first episode occurred in the referring hospital. Approximately 80% of infants with hypoglycemia also had an episode of hyperglycemia. After adjusting for the severity of HIE, hypoglycemia remained significantly associated with more severe brain injury on early MRI, lower IQ scores, and a higher rate of adverse outcomes at preschool age. Although it is not possible to determine whether the relationship between hypoglycemia and brain injury is causal from this exploratory analysis, these results suggest that hypoglycemia might aggravate the effects of perinatal asphyxia on the neonatal brain.

Previous studies on infants with asphyxia with HIE who received therapeutic hypothermia defining hypoglycemia as blood glucose of less than 46.8 mg/dL have reported incidences between 23.1% and 31.1% within the first days after birth.[5,7,9] Differences in blood glucose management guidelines and the presence of predisposing factors for hypoglycemia, including birth weight and maternal disease, between our study population in comparison with others may be responsible for the higher incidence demonstrated in this study. Furthermore, most studies assessed glucose measurements during the initial days after birth, whereas in this study all measurements before neuroimaging or death were analyzed. Tan et al reported an incidence of 31.1% for hypoglycemia before and during therapeutic hypothermia among infants with HIE.[5] Infants with HIE were started on a higher maintenance glucose infusion and hypoglycemia was treated more aggressively compared with our center, with a glucose of less than 46.8 mg/dL as the threshold for the administration of a glucose bolus and increasing the maintenance infusion. Two other studies reported incidences of 25% and 23.1% for hypoglycemia among infants cooled for HIE, but did not describe details of the glucose management guidelines or maternal characteristics.[7,9] Almost 80% of infants in our study had hyperglycemia, which is high in comparison with other studies on cooled newborns with asphyxia.[4,6,14] In contrast with some other centers, insulin is rarely offered to term infants in our NICU.[6] Despite increasing evidence for the association of hyperglycemia with adverse outcome, there still seems to be the tendency to treat hypoglycemia more aggressively than hyperglycemia.[4,14] Furthermore, in 78.1% of infants with both hypoglycemia and hyperglycemia, the episode of hypoglycemia occurred first, suggesting that the episode of hyperglycemia might have been the result of an intervention to increase glucose levels.

A variation of injury patterns has been associated with hypoglycemia on early MRI. A study of infants with symptomatic hypoglycemia without evidence of asphyxia and encephalopathy reported white matter injury in 94%, in which 43% was severe.[36] Additional abnormalities included a posterior pattern, cortical involvement, hemorrhage, basal ganglia and thalamus injury, and middle cerebral artery infarction. Other studies with heterogeneous cohorts reported injury predominantly located in the parietal-occipital lobes.[37,38] Wong et al reported that, in infants with neonatal encephalopathy, posterior white matter and pulvinar injury were most predictive of symptomatic hypoglycemia superimposed on the predominant pattern of injury seen in HIE.[39] A watershed pattern was most often seen, associated with severe hypoglycemia. Whether these infants received therapeutic hypothermia is unknown. Martinez-Biarge et al reported that in noncooled infants with asphyxia with HIE hypoglycemia was more common among those with severe white matter injury.[11] To the best of our knowledge, only 1 previous study assessed MRI abnormalities in infants with asphyxia with hypoglycemia in the context of therapeutic hypothermia. The authors reported that cooled infants with hypoglycemia within 24 hours after birth had a higher adjusted odds of watershed or focal-multifocal strokes compared with infants with normal glucose levels.[6] In agreement with these findings, our data

Table III. Neurodevelopmental outcome of the infants with and without hypoglycemia at 2 and 5.5 years of age, univariable analysis

Outcomes	Hypoglycemia (total n = 65; 2-year outcome n = 53; 5.5-year outcome n = 34)		No hypoglycemia (total n = 122; 2-year outcome n = 100; 5.5-year outcome n = 68)		*P* value
	Available for n (%)	Median (IQR) or n (%)	Available for n (%)	Median (IQR) or n (%)	
At 2 years of age					
Bayley-III-NL cognitive composite score	44 (83.0)*	103 (19)	83 (83.0)*	105 (19)	.114
Bayley-III-NL motor composite score	42 (79.2)*	108 (15)	79 (79.0)*	112 (17)	**.028**
Adverse outcome					
Total	62 (95.4)	21 (32.3)	117 (95.9)	31 (25.0)	.246
Death before discharge	65 (100)	12 (18.5)	122 (100)	22 (17.7)	.831
Cerebral palsy	65 (100)	2 (3.1)	122 (100)	4 (3.2)	.941
Neurodevelopmental delay†	65 (100)	5 (7.7)	122 (100)	4 (3.2)	.169
Severe hearing or visual impairment	65 (100)	2 (3.1)	122 (100)	1 (0.8)	.242
At 5.5 years of age					
M-ABC-2 total score percentile	28 (82)	16 (44)	59 (87)	25 (34)	**.014**
M-ABC-2-NL total score ≤5th percentile	28 (82)	10 (29)	59 (87)	7 (10)	**.009**
WPPSI-III-NL,					
Total IQ, median (IQR)	27 (79)	94 (29)	57 (84)	105 (21)	**.042**
Total IQ ≤85	27 (79)	7 (21)	57 (84)	7 (10)	.130
Verbal IQ, median (IQR)	27 (79)	93 (28)	55 (81)	104 (17)	.112
Verbal IQ ≤85	27 (79)	7 (21)	55 (81)	7 (10)	.120
PIQ, median (IQR)	27 (79)	98 (24)	55 (81)	107 (19)	**.023**
PIQ ≤85	27 (79)	6 (18)	55 (81)	5 (7)	.165
Processing speed, median (IQR)	25 (74)	88 (27)	54 (79)	100 (18)	**.007**
Processing speed ≤85	25 (74)	12 (35)	54 (79)	8 (12)	**.002**
Adverse outcome in survivors, n (%)	29 (85)	20 (59)	59 (87)	22 (32)	**.005**

Significant *P* values are set in bold.
*Percentage based on survivors.
†Defined as GMDS developmental quotient <88, or Bayley-III-NL motor or cognitive composite score ≤85.

demonstrated a higher rate of moderate-severe WM/WS injury in the hypoglycemia group. A moderate-severe basal ganglia and thalamus pattern of injury was more common among the nonhypoglycemic group. We speculate that hypoglycemia in particular affects the white matter and watershed regions, thereby resulting in a greater proportion of moderate-severe WM/WS and near total injury in the hypoglycemia group. Infants with near total injury may possibly only have shown a moderate-severe basal ganglia and thalamus pattern of injury without hypoglycemia.

Our study allowed us to compare the outcome of cooled asphyxiated infants with and without hypoglycemia at preschool age. Previous papers have assessed the outcome at 12-24 months. Montaldo et al demonstrated that a longer duration of hypoglycemia and a greater area under the hypoglycemic curve were associated with an adverse neurodevelopmental outcome at 18-24 months in infants with asphyxia receiving therapeutic hypothermia.[4] Another study showed that early recurrent hypoglycemia was associated with an increased risk of death or severe disability in cooled infants with asphyxia.[5] A study of infants at risk for encephalopathy, with 12% receiving therapeutic hypothermia, reported that hypoglycemia was associated with worse cognitive and motor outcome at 12 months.[40] A post hoc analysis of the CoolCap trial, with 50% receiving therapeutic hypothermia, showed that an adverse outcome at 18 months was more common among neonates with a blood glucose of 40 mg/dL or less.[14] In our study, the 2-year cognitive and motor scores were in the normal range, and in the multivariable analysis hypoglycemia was not associated with worse motor and cognitive scores

Table IV. Multivariable analysis of hypoglycemia or hyperglycemia adjusted for aEEG background pattern on admission: regression coefficients (B) and aORs for MRI injury, 2-year and 5.5-year neurodevelopmental outcomes

Variables	Hypoglycemia		Hyperglycemia	
	B or aOR (95% CI)	*P* value	B or aOR (95% CI)	*P* value
Total MRI injury score	3.6 (0.8 to 6.4)	**.011**	2.4 (−1.0 to 5.7)	.164
Bayley-III-NL cognitive composite score	−3.9 (−9.1 to 1.3)	.143	1.3 (−4.5 to 7.1)	.658
Bayley-III-NL motor composite score	−4.2 (−8.9 to 0.5)	.081	2.7 (−2.6 to 8.0)	.312
Adverse outcome at 2 years of age*	1.9 (0.9 to 4.2)	.088	1.6 (0.6 to 4.8)	.365
Adverse outcome in survivors at 2 years of age*	2.1 (0.8 to 5.7)	.154	1.0 (0.3 to 3.6)	.957
M-ABC-2-NL	−11.7 (−24.7 to 1.4)	.079	−7.6 (−22.1 to 6.8)	.279
WPPSI-III-NL total IQ	−9.2 (−17.1 to −1.3)	**.023**	−7.7 (−16.7 to 1.2)	.090
Adverse outcome at 5.5 years of age*	3.6 (1.4 to 9.0)	**.007**	2.8 (1.0 to 7.9)	.052
Adverse outcome in survivors at 5.5 years of age	3.5 (1.3 to 9.2)	**.011**	2.5 (0.8 to 7.6)	.097

Significant *P* values are set in bold.
*Including infants who died before discharge.

or adverse outcome at 2 years of age, independent of HIE severity. However, at preschool age, a univariable analysis showed worse cognitive and motor function in the hypoglycemia group, which remained significant for cognitive function after adjustment for HIE severity in our multivariable model. It is to be expected that the difference in cognitive abilities may become even clearer at school age, when cognitive deficits associated with WM/WS injury often first become apparent. Furthermore, our data showing higher rates of abnormalities of the mammillary bodies among infants with hypoglycemia, and worse verbal IQ scores in infants with hypoglycemia with abnormal mammillary bodies, suggest that these infants are at increased risk for neurocognitive impairments later in life, as a recent study has reported a strong association between mammillary body atrophy with episodic memory and neurocognitive outcome at 10 years of age.[17] These findings all strongly support neurodevelopmental follow-up beyond 24 months of age. Infants with hypoglycemia had higher lactate levels on admission, possibly owing to a higher rate of anaerobic glycolysis.[41] This finding could indicate that asphyxia was more severe in the hypoglycemic group, leading to worse neurodevelopmental outcomes. However, pH and Apgar scores, other indicators for the severity of perinatal asphyxia, were comparable between the groups.

Several studies have reported that hyperglycemia is associated with worse brain function on aEEG, microstructural changes of the brain, and adverse neurodevelopmental outcome.[4,14,42,43] Tam et al demonstrated that in infants with encephalopathy, of whom 95% received therapeutic hypothermia, higher maximum glucose levels on the first day after birth were associated with microstructural changes in mean diffusivity on using diffusion tensor imaging, while lower minimum glucose levels were not associated with microstructural changes.[43] Noteworthy, the mean minimum glucose of the cohort on the first day after birth was within the normal range and the mean maximum glucose level was more than 144 mg/dL. Strict protocols to avoid hypoglycemia may have minimized the occurrence and duration of hypoglycemia and limited researchers from detecting diffusion changes for the infants with hypoglycemia. Basu et al observed an unadjusted association between hyperglycemia and predominant basal ganglia injury, which was not significant after adjusting for covariates.[6] In a post hoc analysis of the CoolCap Study, it was concluded that hypoglycemia and hyperglycemia were both associated with adverse outcome at 18 months of age, independent of hypothermia treatment and HIE severity based on Sarnat staging.[14] In our study, hyperglycemia was not independently associated with a higher degree of brain injury on MRI or worse outcomes. We used aEEG on admission to adjust for HIE severity, because of the possibility to retrospectively grade aEEG background patterns, and as in our hands neuromonitoring is more objective than clinical grading tools. Hyperglycemia may be a marker for worse HIE, owing to the release of stress hormones and decreased metabolism in injured brain tissue.[44] However, after adjustment for HIE severity, the odds of an adverse outcome at preschool age were close to being significantly higher for infants with hyperglycemia when those who died before discharge were also included, suggesting that hyperglycemia independently influences outcome. Only 13 infants showed hypoglycemia without also experiencing hyperglycemia. Hepatic dysfunction and pancreatic islet hypoxic-ischemic changes described after perinatal asphyxia may cause unstable glucose levels.[45,46] Previous studies have suggested that infants with both hyperglycemia and hypoglycemia have worse brain injury.[6] The European guidelines on newborn resuscitation recommend monitoring and treatment of infants requiring significant resuscitation to prevent hypoglycemia and large swings in blood glucose levels, but the optimal glycemic concentration in infants with asphyxia is unknown.[47] In our study, the presence of both hyperglycemia and hypoglycemia was independently associated with worse cognitive scores at 2 years, but not at preschool age, which suggests that hypoglycemia might be the most important factor with regard to long-term outcome. However, only a limited number of infants in our study population had reached preschool age. Our results emphasize the need for further studies to establish the ideal blood glucose levels in infants with HIE receiving therapeutic hypothermia and to assess the association of hyperglycemia with and without hypoglycemia on brain injury and long-term outcome.

The strengths of this study include the substantial homogeneous study sample, with all infants receiving therapeutic hypothermia, the use of a comprehensive score to describe MRI features, and the careful assessment of outcomes at 2 and 5.5 years using validated instruments. Our study has several limitations. Because most infants were born in a level II hospital, information on maternal medication use and glucose management before admission at our NICU might have been incomplete, and an area under the hypoglycemic curve could not be calculated. The incidence of hypoglycemia may have been underestimated, because glucose was not measured continuously. It is important to highlight that our results on MRI injury and outcomes are based on data from infants who were less severely affected than the overall group of infants with asphyxia receiving therapeutic hypothermia, because the most severely affected infants died before an MRI could be performed, and motor and cognitive scores at 2 and 5.5 years of age only represent survivors.

Although it is not possible to conclude from this exploratory analysis whether the association between hypoglycemia and brain injury is causal, our results suggest that hypoglycemia might aggravate the effects of perinatal asphyxia. Adequate anticipation and treatment to avoid large swings in glucose levels in infants with asphyxia receiving therapeutic hypothermia is crucial to minimize brain injury and neurodevelopmental sequelae. Additional studies to investigate the association of hyperglycemia with and without hypoglycemia on brain injury and long-term outcome, and the optimal glucose levels in these newborns are warranted. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Genetic Etiology of Syndromic Congenital Hearing Loss

Konigsmark BW. Hereditary childhood hearing loss and integumentary system disease. J Pediatr 1972;80:909-19.

In 1972, Konigsmark discussed 14 syndromes of genetic congenital hearing loss, with 7 associated with skin pigmentation changes. Each syndrome was hypothesized to have a genetic etiology based on the observed familial inheritance, either autosomal or sex-linked and displayed variable expressivity.

Fifty later more than 400 genetic syndromes associated with hearing loss have been described with over 110 causative genes identified.[1] Several of the syndromes discussed by Konigsmark have been combined, while others, such as recessive albinism and congenital hearing loss, have been attributed to coincident inheritance of 2 separate recessive disorders. The genetic etiologies of the other syndromes have been identified.

Waardenburg syndrome, the most common cause of syndromic congenital hearing loss, has been found to be mainly attributable to *PAX3* mutations.[1] Noonan syndrome with multiple lentigines is attributed to *PTPN11* mutations. The *PAX3* gene encodes a protein, which induces the neural crest cell border at the neural plate, thus impacting neural crest cell migration and further differentiation. *PTPN11* codes for an intracellular protein involved in the RAS signaling pathway, integral for cardiogenesis, hematopoiesis, and other intracellular pathways.

Dominant knuckle pads, leukonychia, and hearing loss (known as Bart-Pumphrey syndrome) and dominant keratopachydermia with hearing loss (known as Vohwinkel syndrome) have been attributed to mutations in the *GJB2* gene, which encodes connexin 26 protein. This protein helps form gap junctions and maintains potassium homeostasis in proximity to cochlear hair cells during auditory transduction. Connexin 26 was found to be absent in skin from an affected family member. Dominant onychodystrophy and congenital hearing loss has been attributed to *ATP6V1B2* mutation. This gene encodes an ATPase proton pump which mediates acidification of intracellular organelles necessary for protein sorting and endocytosis.

Recessive onychodystrophy and congenital deafness (known as DOOR Syndrome) is caused by *TBC1D24* gene mutations, which regulates the transport of intracellular vesicles. Familial pili torti and nerve deafness is caused by *BCS1L* gene mutations, which codes for mitochondrial complex III necessary for oxidative phosphorylation.[2]

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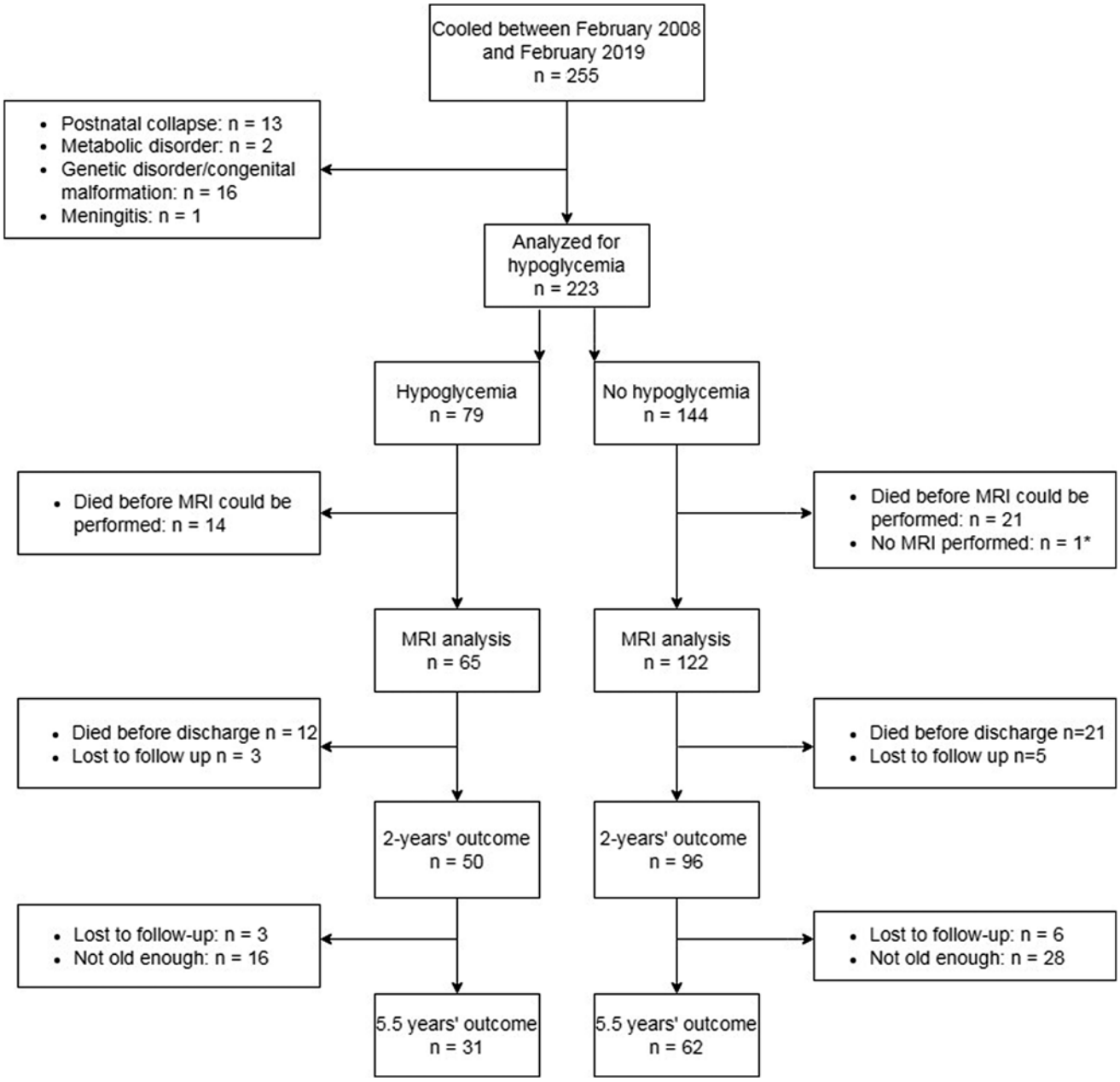

Figure. Flowchart of the study population. *In 1 infant, MRI was not performed because of transfer to another hospital for extracorporeal membrane oxygenation.