

Early Hyperglycemia in Very Preterm Infants Is Associated with Reduced White Matter Volume and Worse Cognitive and Motor Outcomes at 2.5 Years

Nima Naseh^a Nuno Canto Moreira^b Tânia F. Vaz^c Karla Gonzalez Tamez^a
Hugo Ferreira^c Ylva Fredriksson Kaul^a Martin Johansson^a Barbro Diderholm^a
Fredrik Ahlsson^a Johan Ågren^a Lena Hellström-Westas^a

^aDepartment of Women's and Children's Health, Uppsala University, Uppsala, Sweden; ^bDepartments of Neuroradiology, Uppsala University Hospital and Karolinska University Hospital, Uppsala, Sweden; ^cFaculty of Sciences, Institute of Biophysics and Biomedical Engineering, University of Lisbon, Lisbon, Portugal

Keywords

Brain injury · Impairment · Insulin · Magnetic resonance imaging · Neurodevelopment

Abstract

Introduction: Hyperglycemia in very preterm infants is associated with increased morbidity and mortality. We aimed to investigate potential associations between early hyperglycemia, neonatal cerebral magnetic resonance imaging (MRI), and neurodevelopment at 2.5 years. **Methods:** The study population included 69 infants with gestational age (GA) 22.3–31.9 weeks ($n = 29$ with GA <28 weeks), born 2011–2014. Plasma glucose concentrations during the first week were checked according to clinical routines. Hyperglycemia was defined as glucose concentrations above 8.3 mmol/L (150 mg/dL) and above 10 mmol/L (180 mg/dL), respectively, categorized as the highest glucose days 0–2, number of days above 8.3 and 10 mmol/L, and prolonged (yes/no) 2 days or more above 8.3 and 10 mmol/L. The MRI analysis included morphological assessment, regional brain volumes, and assessment of apparent diffusion coefficient (ADC). Neurodevelopmental impairment (NDI) developed in 13 of 67 infants with available outcomes, of which 57 were

assessed with the Bayley-III. Univariate and multiple linear and logistic regressions were performed with adjustments for GA, birth weight z-scores, and illness severity expressed as days on mechanical ventilation. **Results:** Hyperglycemia above 8.3 mmol/L and 10 mmol/L was present in 47.8% and 31.9% of the infants. Hyperglycemia correlated independently with lower white matter volume, but not with other regional brain volumes, and was also associated with lower ADC values in white matter. Hyperglycemia also correlated with lower Bayley-III cognitive and motor scores in infants with GA <28 weeks, but there was no significant effect on NDI. **Conclusion:** Early hyperglycemia is associated with white matter injury and poorer neurodevelopment in very preterm infants.

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Introduction

Early hyperglycemia develops in 20–80% of very preterm (VPT) infants and is associated with severe neonatal morbidities and increased mortality [1–7]. The pathogenesis of hyperglycemia in VPT infants is only partly understood but may include the inability to respond to

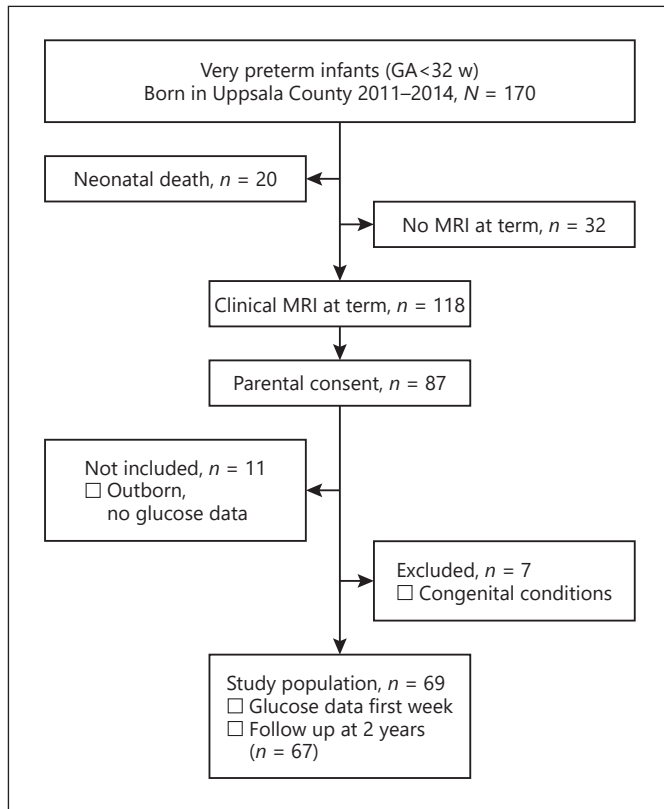


Fig. 1. Flowchart of the study population. Cerebral MRI examinations were recommended to parents as a clinical routine for VPT infants with GA less than 32 weeks in Uppsala County during the time period 2011–2014.

glucose infusion with suppressed glucose production, low insulin production, and insulin resistance [8–10]. Consequently, early enhanced parenteral nutrition has also been linked to increased risk for hyperglycemia [11–13]. Although several studies have demonstrated the risks associated with hyperglycemia, insulin treatment has not been associated with clear benefits [14]. Little is known about the long-term consequences of hyperglycemia in surviving VPT infants, although available data indicate an increased risk for adverse outcomes [15, 16]. Furthermore, since most studies have focused on extremely low birth weight or extremely preterm (EPT) infants, i.e., with a gestational age (GA) <28 weeks, less is known about potential effects of hyperglycemia in more mature VPT infants (GA <28–31 weeks).

We hypothesized that hyperglycemia in infants may have adverse effects on brain development and also that the effects could vary depending on the infants' maturity at birth. Consequently, the objectives of the present study

were to investigate associations between early hyperglycemia and brain development as assessed by cerebral magnetic resonance imaging (MRI) at term equivalent age and to evaluate potential long-term effects of hyperglycemia on neurodevelopment.

Methods

During the time period July 1, 2011, to December 31, 2014, cerebral MRIs were performed at term equivalent age as part of the clinical routines for VPT infants treated in the Neonatal Intensive Care Unit (NICU) at Uppsala University Hospital, a tertiary referral center in Sweden. In total, 170 VPT infants were born in Uppsala County during the time period, of which 20 died. MRIs were performed in 118 of the 150 surviving infants. The main reason for not performing a MRI examination was parental decline, since repeated head ultrasounds were also performed routinely. Parental permissions to participate in the overall evaluation of the MRI examinations were obtained for 87 of the 118 infants (Fig. 1). In the present study, data from 18 infants were excluded since 11 were initially cared for in other hospitals and seven had congenital conditions (genetic syndromes, malformations, congenital infection). Thus, the final study population included 69 infants with GAs ranging from 22.3 to 31.9 weeks, and birth weights from 415 to 2,094 g (see Table 1 for clinical characteristics). None of the infants in the study received insulin or postnatal steroids.

Prospectively collected neonatal data from the Swedish Neonatal Quality register were merged with data from patient records, including all plasma glucose (P-glucose) results ($n = 926$) from the first week of life (days 0–6), and clinical outcomes at 2.5 years' corrected age. The data variables included any antenatal steroid exposure; antenatal steroids less than 24 h prior to delivery; mode of delivery; GA in days, the two GA subgroups EPT (GA <28 weeks) and VPT (GA 28–31 weeks); birth weight; birth weight z-score; Apgar score; sex; measures of illness severity (surfactant administration, days on mechanical ventilation); hospital morbidities (intraventricular hemorrhage [IVH] and white matter injury as graded on MRI); treatment for persistent ductus arteriosus (PDA); bronchopulmonary dysplasia; sepsis defined as the presence of clinical symptoms and positive blood culture or clinical sepsis with symptoms and raised C-reactive protein; necrotizing enterocolitis; and retinopathy of prematurity (ROP, grade).

Glucose Data

All P-glucose samples were analyzed at point of care using an automated blood gas analyzer (ABL 800, Radiometer, Denmark, UK). The subsequent analyses included the highest and lowest glucose concentrations for each day during the first week (days 0–6) and during the first 3 days (days 0–2). Based on data in previous studies (1–6), two levels of hyperglycemia were specified: P-glucose >8.3 mmol/L (>150 mg/dL) and >10 mmol/L (>180 mg/dL), and the number of days during the first week that glucose concentrations exceeded these levels. Prolonged hyperglycemia was defined as glucose concentrations >8.3 or >10 mmol/L for two or more consecutive days. In addition, hypoglycemia was defined as a P-glucose <2.6 mmol/L (<46 mg/dL), and prolonged hypoglycemia defined as a P-glucose <2.6 mmol/L for two or more days.

Table 1. Patient characteristics for 69 surviving VPT infants who were investigated for effects of early neonatal hyperglycemia

	All infants with GA <32 weeks (n = 69)	EPT infants, GA <28 weeks (n = 29)	VPT infants, GA 28–31 weeks (n = 40)
Antenatal steroids	62 (89.9)	28 (96.6)	34 (85)
Cesarean section	45 (69.2)	15 (51.7)	30 (75)
GA in weeks	28.3 (2.7)	25.5 (1.3)	30.3 (1.2)
Birth weight in grams	1,178 (420)	810 (175)	1,445 (374)
Male	31 (44.9)	10 (34.5)	21 (52.5)
5-min Apgar score	8 (1.5)	7.3 (1.5)	8.5 (1.3)
Mechanical ventilation, days	1 (0–82)	10 (0–82)	0 (0–10)
Sepsis	21 (30.4)	15 (51.7)	6 (15)
PDA treated	17 (24.6)	17 (58.6)	0
ROP grade 1–3	20 (28.9)	16 (55.1)	4 (10)
No IVH on MRI	49 (71)	19 (65.5)	30 (75)
IVH grade 1 on MRI	13 (18.8)	6 (20.7)	7 (17.5)
IVH grade 2 on MRI	7 (10.1)	4 (13.8)	3 (7.5)
White matter injury on MRI	5 (7.2)	2 (6.9)	3 (7.5)
P-glucose >8.3 mmol/L	33 (47.8)	25 (86.2)	8 (20)
P-glucose >10 mmol/L	22 (31.9)	16 (55.2)	6 (15)
P-glucose <2.6 mmol/L	38 (55.1)	13 (44.8)	25 (62.5)
Bayley-III cognitive index	102.5 (14.3) (n = 57)	100.2 (13.9) (n = 22)	104 (14.5) (n = 35)
Bayley-III motor index	100.9 (12) (n = 47)	97.4 (10.5) (n = 18)	103 (12.6) (n = 29)
Bayley-III language index	101.6 (16) (n = 56)	102.7 (18.8) (n = 22)	100.7 (15.3) (n = 34)
NDI	13 (19.4) (n = 67)	8 (28.6) (n = 28)	5 (12.8) (n = 39)

Data are given for the whole study population (n = 69) and for EPT infants with GA <28 weeks and VPT infants with GA 28–31 weeks separately. Data are shown as numbers (percentages) and mean (SDs). Days on mechanical ventilation are given as median (range). PDA, persistent ductus arteriosus; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage, no infant had IVH grade 3 or 4; MRI, magnetic resonance imaging; Bayley-III, Bayley Scales of Infant Development, version III.

MRI Analysis

The MRIs were performed according to clinical routines at a mean and standard deviation (SD) postmenstrual age of 40.1 (1.6) weeks on a 1.5 T Siemens Avanto (Siemens, Erlangen, Germany) scanner with use of a neonatal-adapted imaging protocol including T2-weighted fast spin echo, T2*-weighted gradient echo, volumetric T1-weighted and diffusion-weighted imaging (single-shot EPI sequences, b value = 0 and 800 s/mm²). The MRI evaluation included a systematic visual scoring of the supra- and infratentorial brain structures with assessment of IVH, white matter injury [17], ventricular dilatation, basal ganglia injury, and cerebellar hemorrhages. Apparent diffusion coefficients (ADCs) were computed from the diffusion-weighted imaging data and measured in the left periventricular white matter, left basal ganglia, and the pons. The ADC measurements were carried out by freehand drawing of circle-shaped regions of interest with a radius of 10 mm (white matter), 9 mm (basal ganglia), and 6 mm (pons). The two assessors (NN and NCM) were blinded for clinical characteristics and outcomes. Quantification of brain volumes was performed using a semiautomated segmentation, Morphologically Adaptive Neonatal Tissue Segmentation [18] including total brain volume; white matter volume; cortical gray matter volume; deep nuclear gray matter volume; and cerebellar volume.

Neurodevelopmental Assessment

The Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III), was used for neurodevelopmental assessment at 2.5 years in 57 children (cognitive index n = 57, language index n = 56, motor index n = 47). In 10 of the remaining 12 children, the results of clinical neurodevelopmental assessments by a pediatrician were available at 2.5 years or later, but without formal test results. Two children were lost to follow-up. A dichotomous variable, neurodevelopmental impairment (NDI), was created that included children with a diagnosis of neurodevelopmental delay (including cerebral palsy) or a score below 85 on at least one Bayley-III index, according to currently recommended cutoffs [19].

Statistical Analysis

Descriptive statistics (mean, SD, median, range) and parametric and nonparametric tests were used for comparisons, as appropriate. The analyses were also performed separately for the two subgroups EPT (GA <28 weeks) and VPT (GA 28–31 weeks). Univariate and multiple linear regressions were performed for assessing relations between glucose levels and clinical variables in relation to MRI and 2.5-year outcome.

The multiple regression analyses of the relations between glucose concentrations and levels (independent variables), and MRI

(regional brain volumes and ADC values) (dependent variables) were adjusted for clinical factors that were consistently and significantly (p value <0.05) associated with hyperglycemia and MRI findings, i.e., GA, birth weight z-scores, and days on mechanical ventilation (covariates), and also for postmenstrual age in weeks at the time for the MRI examination. Tests of collinearity showed that GA and birth weight had very similar associations; consequently, birth weight z-scores were chosen together with GA for the multiple regression analyses.

Similarly, the multiple regression analyses assessing glucose concentrations associated with Bayley-III scores, and the binary logistic regressions for evaluating NDI in relation to glucose levels, were adjusted for GA, birth weight z-scores, and days on mechanical ventilation. The Statistical Package for Social Sciences version 25 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

Clinical data are presented in Table 1 for the full cohort ($n = 69$) and for the two subgroups. Five infants required surgery for PDA, one infant had necrotizing enterocolitis, and one infant was treated for ROP. The MRI examinations showed no IVH in 49 infants, IVH grade 1 in 13 and grade 2 in 7 infants. One infant had a small cerebellar hemorrhage. Diffuse or cystic white matter injury was present in five children. At 2.5 years, six children who were already diagnosed with NDI (cerebral palsy, $n = 3$, and neurodevelopmental delay and autism, $n = 3$) were not tested with the Bayley-III. Seven children scored below 85 on at least one Bayley-III index score, and in total, 13/67 (19.4%) children were classified as having NDI.

Glucose

The mean (SD) number of blood samples per infant during the first 3 days was 8.1 (3.8), and the total number of samples during the first week was 926. Thirty-three (47.8%) infants developed hyperglycemia >8.3 mmol/L, and 22 (32%) had glucose concentrations >10 mmol/L. Prolonged hyperglycemia above >8.3 mmol/L or >10.0 mmol/L was present in 20 (69%) and 15 (51.7%) of the 29 EPT infants, and in 6 (15%) and 4 (10%) of the 40 VPT infants. Hypoglycemia <2.6 mmol/L was usually brief, and in 24 of the 31 infants (44.9%) with hypoglycemia, it only occurred on the day of birth. Five VPT infants (7.2%) had hypoglycemia for more than one day (four infants during 2 days, and one infant for 5 days, in spite of treatment).

Magnetic Resonance Imaging

The mean (SD) brain volumes were total brain volume 379 (45) mL, white matter volume 111 (25) mL, cortical

gray matter volume 201 (38) mL, deep nuclear gray matter volume 29 (4) mL, and cerebellar volume 26 (4) mL. Only the white matter volume differed between the two GA groups and was significantly lower in the EPT infants, 99 (21) mL, versus 121 (24) mL in the VPT infants, $p < 0.001$ (unadjusted). The mean (SD) ADC values (10^{-6} mm²/s) were 1,420 (138) in the white matter, 1,976 (63) in basal ganglia, and 983 (134) in the pons with no significant differences between the two GA groups.

Associations between Neonatal Variables, MRI, and Neurodevelopment

In univariate regression analyses, several of the used definitions of hyperglycemia related significantly ($p < 0.05$) to neonatal characteristics, including GA, birth weight, birth weight z-scores, sepsis, IVH grade, white matter injury, ROP grade, and days on mechanical ventilation. However, antenatal steroids, mode of delivery, 5-min Apgar score, infant sex, surfactant administration, PDA, and bronchopulmonary dysplasia were not associated with hyperglycemia.

Several clinical variables (GA, birth weight z-score, BW, infant sex, sepsis, IVH, white matter injury, degree of ROP, days on mechanical ventilation) and indicators of hyperglycemia had significant univariate correlations with reduced brain volumes, including white matter volume and total brain volume, and with ADC values in the basal ganglia and white matter. However, in univariate regressions, birth weight z-scores were only correlated to white matter ADC. In the EPT subgroup, the univariate associations between hyperglycemia and brain volumes were only significant for white matter volume. In the EPT group, significant univariate associations were present between hyperglycemia variables and MRI white matter volume, deep nuclear gray matter volume, cerebellar volume, and total brain volume, and also with ADC in the white matter and basal ganglia.

Several clinical variables including GA, BW, IVH, days on mechanical ventilation, ROP grade, and indicators of hyperglycemia had significant univariate associations with the Bayley-III cognitive and motor indices, but not with the Bayley-III language index or with the dichotomous variable NDI. For the multiple regression analyses (Table 2), the hyperglycemia levels that were consistently associated with neonatal characteristics, reduced brain volumes, and lower Bayley-III scores in the univariate analyses were chosen for further evaluation. These were (a) the highest glucose concentration on days 0–2; (b) the number of days with hyperglycemia (>8.3 mmol/L and >10 mmol/L); and (c) prolonged hyperglycemia (>8.3

Table 2. Associations between hyperglycemia (days 0–6) and cerebral MRI at term equivalent age in a cohort of 69 VPT infants

	White matter volume, mL		Total brain volume, mL		ADC white matter		ADC basal ganglia	
	regression coefficient (95% CI)	p value	regression coefficient (95% CI)	p value	regression coefficient (95% CI)	p value	regression coefficient (95% CI)	p value
All infants with GA <32 weeks (n = 69)								
Highest glucose days 0–2 (mmol/L)	-2.39 (-4.43; -0.36)	0.022	-2.37 (-5.52; 0.77)	0.137	1.49 (-11.59; 14.54)	0.822	1.42 (-5.35; 8.19)	0.676
Prolonged glucose >8.3 mmol/L (yes/no)	-14.39 (-29.51; 0.71)	0.061	-15.33 (-38.45; 7.79)	0.191	16.94 (-69.39; 103.3)	0.694	-2.95 (-47.77; 41.86)	0.895
Prolonged glucose >10 mmol/L (yes/no)	-15.97 (-32.17; 0.23)	0.053	-4.27 (-29.43; 20.89)	0.742	9.83 (-88.12; 107.7)	0.847	20.93 (-29.56; 71.42)	0.418
Glucose >8.3 mmol/L, number of days	-4.29 (-8.81; 0.22)	0.062	-1.26 (-8.26; 5.73)	0.722	-5.29 (-31.43; 20.84)	0.687	-0.027 (-13.59; 13.5)	0.997
Glucose >10 mmol/L, number of days	-4.29 (-8.75; 0.16)	0.059	-1.51 (-8.42; 5.41)	0.665	-16.43 (-42.61; 9.75)	0.214	1.25 (-12.51; 15.01)	0.868
EPT infants with GA <28 weeks (n = 29)								
Highest glucose day 0–2 (mmol/L)	-1.82 (-3.95; 0.31)	0.091	-1.86 (-5.66; 1.95)	0.323	12.24 (-4.75; 29.15)	0.148	5.81 (-5.49; 17.11)	0.294
Prolonged glucose >8.3 mmol/L (yes/no)	-16.47 (-32.32; -0.61)	0.042	-27.19 (-54.54; 0.15)	0.051	87.91 (-21.84; 197.6)	0.114	18.32 (-57.65; 94.3)	0.619
Prolonged glucose >10 mmol/L (yes/no)	-12.79 (-29.51; 3.93)	0.127	-7.18 (-37.17; 22.8)	0.638	118.34 (-1.27; 237.9)	0.052	57.48 (-23.9; 138.9)	0.156
Glucose >8.3 mmol/L, number of days	-1.39 (-7.02; 4.24)	0.625	-1.9 (-11.56; 7.76)	0.694	38.58 (2.4; 74.76)	0.038	14.22 (-11.34; 39.78)	0.258
Glucose >10 mmol/L, number of days	-1.15 (-6.41; 4.11)	0.655	-1.88 (-10.89; 7.13)	0.677	25.28 (-11.85; 62.42)	0.172	20.03 (-3.35; 43.41)	0.089
VPT infants with GA 28–31 weeks (n = 40)								
Highest glucose day 0–2 (mmol/L)	-2.89 (-6.88; 1.1)	0.152	-9.96 (-8.4; 4.48)	0.542	-2.23 (-24.49; 20)	0.845	-1.96 (-10.62; 6.71)	0.656
Prolonged glucose >8.3 mmol/L (yes/no)	-6.29 (-32.06; 19.48)	0.626	7.49 (-33.07; 48.05)	0.715	-49.28 (-187.7; 89.13)	0.477	-28.14 (-81.67; 25.39)	0.292
Prolonged glucose >10 mmol/L (yes/no)	-21.34 (-51.38; 8.71)	0.158	8.48 (-40.16; 57.11)	0.725	-112.4 (-275.8; 51.1)	0.171	-42.48 (-106.4; 21.45)	0.185
Glucose >8.3 mmol/L, number of days	-4.74 (-11.92; 2.44)	0.188	1.37 (-10.21; 12.95)	0.813	-26.51 (-64.8; 11.78)	0.168	-14.32 (-28.84; 0.2)	0.053
Glucose >10 mmol/L, number of days	-7.94 (-15.86; -0.02)	0.049	2.05 (-11.16; 15.26)	0.733	-50.72 (-92.17; -9.27)	0.018	-25.39 (-40.53; -10.25)	0.002

The multiple regression analyses were adjusted for GA, days on mechanical ventilation, birth weight z-score, and postmenstrual age at the MRI examination. Significant and near-significant associations are given in bold. No infant received insulin or postnatal steroids. "Prolonged" was defined as duration of 2 days or more. ADC, apparent diffusion coefficient.

Table 3. Associations between early hyperglycemia and 2.5-year outcome (Bayley-III cognitive index, $n = 57$, and motor index, $n = 47$) in a cohort of 69 VPT infants and results of multiple regression analyses after adjusting for GA, birth weight z-score, and days on mechanical ventilation

	Bayley-III cognitive index		Bayley-III motor index	
	regression coefficient (95% CI)	p value	regression coefficient (95% CI)	p value
All infants with GA <32 weeks				
Highest glucose day 0–2, mmol/L	-1.18 (-2.59; 0.22)	0.098	-0.68 (-1.94; 0.58)	0.282
Prolonged glucose >8.3 mmol/L (yes/no)	-1.56 (-11.78; 8.66)	0.762	-2.82 (-11.98; 6.34)	0.546
Prolonged glucose >10 mmol/L (yes/no)	0.54 (-10.67; 11.74)	0.924	-5.87 (-16.59; 4.86)	0.288
Glucose >8.3 mmol/L, number of days	-0.68 (-3.76; 2.41)	0.664	-0.93 (-3.84; 1.98)	0.529
Glucose >10 mmol/L, number of days	-1.48 (-4.48; 1.53)	0.328	-2.32 (-5.08; 0.44)	0.097
EPT infants with GA 22–28 weeks				
	($n = 23$)		($n = 19$)	
Highest glucose days 0–2, mmol/L	-2.14 (-4.06; -0.21)	0.032	-1.75 (-3.27; -0.23)	0.027
Prolonged glucose >8.3 mmol/L (yes/no)	-6.12 (-20.38; 8.17)	0.382	-4.27 (-16.27; 7.74)	0.464
Prolonged glucose >10 mmol/L (yes/no)	-6.68 (-21.69; 8.33)	0.366	-8.35 (-22.21; 5.51)	0.222
Glucose >8.3 mmol/L, number of days	-1.85 (-7.09; 3.31)	0.459	-1.92 (-6.57; 2.72)	0.391
Glucose >10 mmol/L, number of days	-3.31 (-7.95; 1.33)	0.157	-4.66 (-8.22; -1.14)	0.014
VPT infants with GA 28–31 weeks				
	($n = 34$)		($n = 28$)	
Highest glucose day 0–2, mmol/L	-0.19 (-2.55; 2.17)	0.872	0.74 (-1.54; 3.02)	0.512
Prolonged glucose >8.3 mmol/L (yes/no)	7.07 (-8.92; 23.05)	0.377	3.59 (-13.19; 20.37)	0.667
Prolonged glucose >10 mmol/L (yes/no)	11.71 (-7.47; 30.88)	0.224	2.96 (-18.55; 24.47)	0.784
Glucose >8.3 mmol/L, number of days	0.76 (-3.74; 5.26)	0.738	0.47 (-4.88; 5.82)	0.867
Glucose >10 mmol/L, number of days	0.04 (-4.95; 5.03)	0.988	-1.01 (-6.69; 8.71)	0.789

The Bayley-III language index did not correlate with hyperglycemia (data not shown). Prolonged hyperglycemia was defined as duration of 2 days or more. Significant associations are given in bold.

mmol/L and >10 mmol/L) for two or more days. In the whole cohort, as well as in the two subgroups separately, the highest glucose concentration on days 0–2 and the dichotomous variable glucose >8.3 mmol/L for 2 days or more (yes/no) had strong independent associations with reduced cerebral white matter volume. White matter organization, as assessed by ADC, was negatively affected by prolonged hyperglycemia, especially in the more mature children (GA 28–31 weeks) who also had negative effects of hyperglycemia on basal ganglia ADC values. In addition, hyperglycemia correlated to Bayley-III lower cognitive and motor indices (Table 3) but only in the EPT infants. Hypoglycemia concentrations or levels were not associated with brain volumes, ADC values, or 2.5-year outcomes (data not shown).

Discussion

The present investigation demonstrated that early hyperglycemia is associated with reduced white matter volume and structural white matter changes at term in infants born VPT (GA <32 weeks) and with poorer cogni-

tion and motor function at 2.5 years in the EPT infants. The associations were stronger for glucose levels above 10 mmol/L and with prolonged hyperglycemia, indicating a dose-response adverse effect.

The associations were different in relation to the infants' maturation. In the EPT infants, hyperglycemia was associated with reduced white matter volume, a borderline significance to reduced total brain volume, and with reduced Bayley-III cognitive and motor indices. In the VPT infants with GA 28–31 weeks, hyperglycemia above 10 mmol/L was associated with reduced white matter volume, but also with ADC results indicating poorer white matter and basal ganglia organization, although there were no associations to later neurodevelopment.

To our knowledge, only one previous study investigated effects of early hyperglycemia on cerebral MRI in EPT infants [3]. The results were comparable to the present study, and hyperglycemia above 8.3 mmol/L on the first day of life was associated with reduced white matter volume at term equivalent age. However, the study did not include long-term follow-up.

A recent Swedish national study of 426 surviving EPT infants supports our findings. In that study, the duration

of neonatal hyperglycemia >8 mmol/L was linearly associated with poorer cognitive and motor scores at 6.5 years. Insulin treatment did not affect the associations [16].

In experimental settings, it has been shown that mechanisms of cerebral injury related to hyperglycemia include microglial activation, neuronal and glial apoptosis; hyperglycemia seems particularly prone to involve the hippocampus and the frontal cortex [20, 21]. In diabetic children, hyperglycemia is considered to be more detrimental for the developing brain than hypoglycemia [22], and asymptomatic hyperglycemia is associated with acute slowing of brain activity on the electroencephalogram [23]. Glucose levels also affect electroencephalogram activity in VPT infants, and high glucose levels were associated with longer inter-burst intervals, i.e., fewer bursts and more depressed brain activity [24]. Early burst activity is important for brain development, and higher burst counts are associated with better brain growth and increased brain volumes at term [25, 26]. The presented MRI data demonstrated potential mechanisms for hyperglycemic brain injury in VPT infants, and hyperglycemia seems to affect both white matter and basal ganglia structure, and white matter growth.

Several studies have assessed the utility of insulin treatment to reduce hyperglycemia in VPT infants, with conflicting results [3, 14, 26–29]. In the context of evaluating potential consequences of hyperglycemia, the expectant strategy in our NICU toward insulin treatment of hyperglycemia of VPT infants is probably a strength. None of the infants received insulin although brief adjustments of infusion rates may have occurred. A Norwegian study identified that an increased risk for hyperglycemia caused by early enhanced nutrition could be reduced by limiting the glucose infusion rates [13].

Although the outcomes in the present investigation strongly support previous studies, and the MRI data also provide potential mechanisms for hyperglycemic brain injury, the retrospective design and the relatively low number of included infants are limitations in our study. Around 40% of the overall VPT population participated in the evaluation. Among the nonparticipants were several very immature infants, including those who died, and also relatively mature infants who declined MRI or follow-up. However, among the infants who performed neonatal MRIs, the children included in this evaluation did not differ in maturation or birth weights from the children who did not participate (data not shown).

In conclusion, in the current study we observed an association between early hyperglycemia in VPT infants and lower white matter volume, structural white matter,

and basal ganglia changes. Hyperglycemia was also associated with poorer neurodevelopment in the EPT infants. The negative effects were related to both the severity and duration of the hyperglycemia.

Statement of Ethics

The investigation was approved by the Uppsala regional ethical review board (Dnr 2014/236), and data were included after written consent from the parents.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Nima Naseh, lead author and neonatologist, collected clinical data, processed the statistics, and assessed MR images. Nuno Canto Moreira, pediatric neuroradiologist, reviewed MRI images. Tania F. Vas, MSc, and Hugo Ferreira, Professor, performed the MRI volumetry assessments and contributed to writing of the manuscript. Karla Gonzalez Tamez, neonatologist, collected glucose data. Ylva Fredriksson Kaul and Martin Johansson, psychologists, tested the children and contributed to statistical processing and writing of the manuscript. Barbro Diderholm and Fredrik Ahlsson, associate professors and neonatologists, contributed to writing of the manuscript. Johan Ågren, associate professor and neonatologist, contributed to the design of the study and significantly contributed to the manuscript. Lena Hellström-Westas, professor and neonatologist, was involved in economy, design, data collection, and statistics and contributed significantly to the manuscripts.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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