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Glutamine effects on brain growth in very preterm children in the first year of life

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SUMMARY

Background & aims: Glutamine supplementation in the neonatal period has been associated with increased brain structure volumes at school-age in very preterm children. The aim of this study was to clarify the emergence and specificity of differences in brain structure volumes, using growth trajectories of head circumference, weight, and length.
Methods: Sixty-five very preterm (<32 weeks gestation) children, who originally took part in a randomized controlled trial on glutamine supplementation, participated. Head circumference, weight, and length, were measured at the neonatal intensive care unit, and at routine follow-up assessments at the outpatient clinic and well baby clinics. Magnetic Resonance Imaging was used to determine brain structure volumes at school-age. Growth trajectories were investigated using multilevel modeling analyses.
Results: Head circumference in the first year of life was positively associated with white matter volume and grey matter volume (range $r = 0.55–0.81$, all $p < 0.002$) at school-age. Furthermore, neonatal glutamine supplementation was associated with increased head circumference growth ($p = 0.008$) in the first year of life, but not with increased growth in weight ($p = 0.44$) and length ($p = 0.73$).
Conclusions: This study indicates a specific increase in head circumference growth in very preterm children that received neonatal glutamine supplementation, and suggests that group differences in brain structure volumes at school-age may have emerged during the first year of life.

1. Introduction

With advances in neonatal intensive care, the survival of very preterm (born <32 weeks of gestation) children has improved considerably. However, a variety of risk factors associated with very preterm birth interfere with normal brain maturation processes,[1,2] eventually affecting overall brain development throughout childhood and adolescence.[3,4] Recently, we found that neonatal glutamine supplementation between day 3 and 30 of life is associated with increased brain structure volumes at school-age in very preterm children.[5] However, these promising findings do not give information whether differences in brain structure volumes indeed originated from the intervention period onwards, nor do they elaborate on the specificity of the differences for brain growth. Alternatively, differences in brain structure volumes at school age may have originated from baseline volume differences between the glutamine and placebo group, or may have resulted from differences in body growth due to variation in nutritional factors, such as a potential higher caloric and/or protein intake in the glutamine group.

In this study, we aimed to clarify the emergence and specificity of differences in brain volumes observed at school-age between very preterm children that received glutamine supplementation or placebo between day 3 and 30 of life. In order to clarify the growth trajectory of brain structure volumes in both groups, we used measures of head circumference. Head circumference growth is rapid in the first year of life, and measures of head circumferences have been shown to be strong predictors of brain volumes and associated neurocognitive functioning in childhood.[6–9] We first elucidated the relation between head circumference in the first year of life and brain structure volumes in very preterm children at school-age. Second, we

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investigated differences in the growth trajectories of head circumference between the glutamine group and the placebo group. Finally, growth trajectories of weight, and length were investigated to clarify whether differences in brain structure volumes at school-age may have originated from differences in nutritional factors associated with growth, such as caloric and protein intake.

2. Methods

2.1. Subjects

A sample of 65 very preterm (<32 weeks gestation) children participated in this study. All very preterm children admitted to the level III neonatal intensive care unit (NICU) of the VU University Medical Center Amsterdam between September 2001 and July 2003 were eligible for inclusion to the randomized controlled trial on the effects of glutamine supplementation.[10] A total of 102 very preterm infants entered the study and received either enteral glutamine supplementation (0.3 g/kg/day) or an isonitrogenous placebo supplementation (alanine) between day 3 and 30 of life. Of the 102 infants included in the original study, 89 infants (87%) were alive at one year of follow-up. At seven years of age, parents were contacted and invited to participate in the current follow-up study collecting data on growth, neurocognition, and brain development, including Magnetic Resonance Imaging (MRI). Data on growth measures were successfully collected for 65 (73%) very preterm children. In addition, MRI follow-up was successful for 52 very preterm children.[5] Nutritional intake during intervention period and number of serious neonatal infections were monitored.[10] Serious infections included sepsis, meningitis, pyelonephritis, pneumonia, and arthritis, were determined using blood, cerebrospinal fluid, and urine cultures as previously described in more detail.[10] Social economic status (SES) was determined by classifying the highest level of education in a household with a number ranging from 1 to 4. A higher number indicated a higher level of education and a corresponding higher SES. Characteristics of the follow-up sample are shown in Table 1. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the medical ethical committee of the VU University Medical Center. Written informed consent was obtained from all subjects.

2.2. Growth measures

Measures of growth, including head circumference (in cm), weight (in kgs), and length (in cm), were collected via three supplementary methods (see Table 2 for an overview). First, growth measures were collected for all very premature children during their stay at the NICU. Second, growth was assessed at multiple standardized follow-up assessments at the hospital and hospital outpatient clinic in the first years of development for 60 very preterm children. For five children, parents did not show up at follow-up appointments. Third, additional data on growth were collected at well baby clinics for 56 very preterm children. In the Netherlands, all children visit a well baby clinic at similar scheduled time points to evaluate their development using standardized

Table 1
Sample characteristics.

	Placebo ($N = 35$)		Glutamine ($N = 30$)		p-value	Effect-size
	Mean	SD	Mean	SD		
General characteristics						
Male gender, *n* (%)	18 (51)		15 (50)		0.91	
Birth weight, kilograms	1.20	0.33	1.27	0.37	0.43	0.19
Birth weight for GA, *z*-value	−0.36	1.38	−0.38	1.91	0.96	0.01
Gestational age, weeks	29.0	1.6	29.7	1.6	0.08	0.44
Head circumference at birth, cm	26.7	2.5	27.5	2.0	0.17	0.35
Head circumference for GA, *z*-value	0.03	1.18	0.08	1.41	0.88	0.04
Social economic status	3.1	0.7	3.3	0.8	0.17	0.27
Clinical characteristics						
Prenatal corticosteroids, *n* (%)	31 (89)		21 (70)		0.06	
Caesarean section, *n* (%)	20 (57)		17 (57)		0.97	
Birth weight <10th percentile, *n* (%)		8 (23)		8 (27)	0.72	
Apgar score after 5 min < 6, *n* (%)		2 (6)		3 (10)	0.52	
1 or more serious infections, *n* (%)		28 (80)		14 (47)	**0.006**	
Number of infections, median (range)		1 (0–3)		0 (0–2)	**0.003**	
Maternal HELLP syndrome, *n* (%)		6 (17)		4 (13)	0.67	
Chorioamnionitis, *n* (%)		11 (31)		7 (23)	0.47	
BPD, *n* (%)		12 (34)		8 (26)	0.51	
IVH grade I/II, *n* (%)		7 (20)		6 (19)	0.99	
IVH grade III/IV, *n* (%)		0 (0)		1 (3)	0.28	
PVL, *n* (%)		3 (9)		1 (3)	0.38	
Nutritional intake characteristics						
Energy day 7 (kcal/kg/day)	94.7	21.2	89.1	17.6	0.25	0.29
Energy day 14 (kcal/kg/day)	111.3	24.6	111.7	15.9	0.94	0.02
Carbohydrates day 7 (mg/kg/day)	8.2	1.6	7.8	1.6	0.32	0.25
Carbohydrates day 14 (mg/kg/day)	8.4	1.5	8.1	0.7	.37	0.26
Proteins day 7 (g/kg/day)	2.9	0.7	2.6	0.6	.14	0.46
Proteins day 14 (g/kg/day)	3.3	0.7	3.4	0.5	.82	0.16
Lipids day 7 (g/kg/day)	3.9	1.4	3.6	1.1	0.39	0.24
Lipids day 14 (g/kg/day)	5.5	1.7	5.7	1.4	0.58	0.13
Breast feeding, *n* (%)		19 (54)		19 (63)	0.46	
Follow-up MRI	($N = 30$)		($N = 22$)			
Age at MRI assessment, years	8.6	0.3	8.6	0.4	.55	0.17
White matter volume, cm^3	466.5	49.2	496.5	60.4	**0.03**	0.54
Grey matter volume, cm^3	705.4	63.3	727.4	85.6	0.39	0.29

Note: BPD = Bronchopulmonary Dysplasia; Maternal HELLP = Hemolysis Elevated Liver enzymes and Low Platelets; IVH = Intraventricular Hemorrhage; PVL = Periventricular Leukomalacia; ROP = Retinopathy of Prematurity.