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Enhanced Nutrient Supply to Very Low Birth Weight Infants is Associated with Improved White Matter Maturation and Head Growth

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Key Words

Premature infants · Growth and nutrition · Brain imaging · Brain maturation · Diffusion tensor imaging · Mean diffusivity

Abstract

Background: Extrauterine growth restriction is common among very low birth weight infants (VLBW, BW <1,500 g). Optimal postnatal nutrient supply is essential to limit growth restriction and ensure adequate growth and neurodevelopment. ***Objectives:*** We compared an enhanced postnatal nutrient supply to a standard supply and evaluated the effects on growth velocity, head circumference growth and cerebral maturation – the latter by magnetic resonance diffusion tensor imaging (DTI). We hypothesized increased growth velocity, head circumference growth and decreased mean diffusivity (MD) in cerebral white matter (WM) areas, suggesting improved cerebral maturation among infants on the enhanced nutrient supply. ***Methods:*** In this randomized controlled trial, infants on the enhanced nutrient supply received increased amounts of energy, protein, fat, essential fatty acids and vitamin A until discharge. DTI was performed close to term equivalent age. Outcomes were growth velocity, head circumference growth and WM mean diffusivity. ***Results:*** Among the 50 included infants, 14 in the intervention group and 11 controls underwent a successful DTI. Infants on the enhanced diet achieved improved growth velocity (16.5 vs. 13.8 g/kg/day, p = 0.01) and increased head circumference (Δz score: 0.24 vs. –0.12, p = 0.15). A significantly lower MD was seen in a large WM area such as the superior longitudinal fasciculi (1.19×10^{-3} vs. 1.24×10^{-3} mm^2/s,

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p = 0.04, adjusted for age when scanned). ***Conclusions:*** Enhanced nutrient supply to VLBW infants is associated with improved growth velocity, increased head circumference growth and decreased regional WM mean diffusivity, suggesting improved maturation of cerebral connective tracts.

Introduction

Preterm infants are at risk of extrauterine growth restriction and impaired neurodevelopment [1]. Approximately 50% of the variance in early postnatal growth can be attributed to nutrition [2]. Much attention has been devoted to improve postnatal growth and development, i.e. optimized nutrition with high amino acid supply [3], different lipid emulsions and supply of essential fatty acids.

Promoting growth with early enhanced nutrient supply is associated with improved cognitive development and brain maturation [4]. Postnatal growth, head growth and magnetic resonance imaging (MRI) findings at 40 weeks' postmenstrual age (PMA) correlate with first-year neurodevelopment [5] and can help predict neurodevelopment among preterm-born infants [6, 7].

Diffusion tensor imaging (DTI) is an MRI technique allowing direct examination of microstructures of the central nervous system, i.e. white matter (WM) tracts. Mean diffusivity (MD) describes the net degree of water displacement in a tissue and is a measure of total diffusion within a voxel. The MD of cerebral connective tracts decreases sharply during brain maturation, where a reduced MD is associated with increased maturation [8]. DTI studies have shown altered cerebral microstructure in preterm-born infants [9] and decreasing MD is seen with increasing age and can be used to detect aberrant WM tracts [10]. Improved postnatal growth is associated with enhanced cognitive development and brain maturation, whereas poor postnatal growth may predict adverse neurodevelopment [11].

To evaluate the impact of a comprehensive nutrient supply on growth velocity, head circumference growth and brain maturation, we performed a randomized controlled trial comparing the effects of enhanced nutrient supply to a standard supply to very low birth weight infants (VLBW, BW <1,500 g) [12, 13]. The intervention group exhibited postnatal growth along their birth percentiles for weight and head circumference, whereas the controls fell off their expected growth trajectories [12]. The main objective of this study was to evaluate brain maturation by DTI among these VLBW infants. We hypothesized decreased WM mean diffusivity among infants receiving the enhanced nutrient supply, suggesting improved cerebral maturation.

Materials and Methods

Design

This study was part of an open randomized controlled trial conducted in three university neonatal intensive care units in Oslo, Norway in 2010. The primary objective was to reduce the proportion of VLBW infants discharged as growth restricted and to achieve growth velocity close to normal fetal growth. Secondary outcomes were development and brain maturation – the latter evaluated using DTI.

The study was approved by the Regional Committee for Medical and Health Research Ethics (ClinicalTrials.gov identifier: NCT01103219). All VLBW infants were eligible for inclusion. Exclusion criteria were congenital malformations, chromosomal abnormalities, critical illness with short life expectancy, and conditions known to affect growth and development. Diagnosis as small for gestational age (weight <10th percentile for age), late-onset septicemia (age >4 days with growth of bacteria in blood culture and clinical signs of septicemia), bronchopulmonary dysplasia (oxygen supplementation at 36 weeks' PMA), severe retinopathy of prematurity (diagnosed by an ophthalmologist), intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia were registered. Sex-specific weight z scores were calculated from a Norwegian reference population and nonsex-specific z scores for head circumference were obtained by Fenton growth chart calculations (http://uccalgary.ca/fenton).

A computer-generated randomization was adopted (stratified by hospital, with blocks of four within each hospital). Sealed opaque envelopes were opened after informed parental consent was obtained.

Nutritional Intervention

Enrollment was performed within 24 h after birth. Infants in the intervention group received an enhanced parenteral and enteral supply of energy, amino acids, lipids, fatty acids and vitamin A. Infants in the control group received a nutrient supply according to recent recommendations [14]. The control group started with 2.0 g/kg/day of amino acids, increasing to 3.6 g/kg/day by day 10. The intervention group started with 3.5 g/kg/day, increasing to 4.4 g/kg/day by day 10. Lipids were increased from 0.5 to 7 g/kg/day by day 10 in the control group and from 2.0 to 8.8 g/kg/day in the intervention group. The control group received the lipid emulsion ClinOleic® (Baxter, Norway), whereas the intervention group received SMOFlipid® (Fresenius Kabi, Norway) to ensure a higher supply of the essential fatty acids docosahexaenoic and arachidonic acid. The supply of proteins and lipids was gradually increased in both groups, mostly by increasing the enteral supply of human milk. Fortification was initiated when 110 ml/kg/day of human milk was tolerated with a gradual increase to 4.2 g Nutriprem® (Nutricia, Norway)/100 ml human milk. The intervention group received an additional enteral supply of amino acids (0.6 g Complete Amino Acid Mix®, Nutricia)/100 ml human milk, docosa-

hexaenoic and arachidonic acid (60 mg/kg/day, Formulaic; Martek, USA) and 1,500 μg/kg/day of vitamin A (Aas Laboratory, Norway). Both groups received equal amounts of fluid and carbohydrates.

Full enteral feeding was defined as 170 ml/kg/day of fortified human milk, which provided 166 kcal/kg/day and 4.4 g protein/kg/day to the intervention group and 146 kcal/kg/day and 3.6 g protein/kg/day to the control group. This difference was estimated to cover cumulative deficits generated during the early postnatal period [2]. The home feeding regime was a combination of human milk (control group) and extra-added 'protein-shots' (1.6 g Complete Amino Acid Mix/20 ml human milk) to the intervention group. The nutritional intervention was continued until 52 weeks' PMA or until the infant exceeded 5.5 kg [12].

MRI Examination

The MRI scans were conducted close to term-equivalent age at a time of day adapted to the infant's circadian rhythm. The infants were fed, settled and wrapped with monitoring equipment attached to them. Heart rate, oxygen saturation and body temperature were monitored during the scan. The MRI scan was performed without the use of sedation with a neonatal nurse and a pediatrician present.

To improve the DTI success rate and to ensure effective noise protection the following three passive attenuators were used: (1) dental putty (Affinis Dental Putty Soft, Coltène Whaledent, Altstätten, Switzerland), (2) pediatric earmuffs (Philips Healthcare, Amsterdam, The Netherlands) and (3) an acoustic hood (Philips Healthcare) placed in the bore of the MRI scanner covering head coil and infant.

An Achieva 3-tesla MRI scanner (Philips Healthcare) with an 8-channel head coil was used. A diffusion-weighted sequence with 62 axial slices was applied (slice thickness = 1.75 mm, field of view = 140 × 140 mm^2, imaging acquisition matrix = 80 × 104, in-plane reconstructed pixel size = 1.59 × 1.63 mm^2, and a sense factor of 2). A total of 15 diffusion-weighted (b value = 700 s/mm^2) and 1 nondiffusion-weighted (b = 0) volumes were collected.

MRI preprocessing analysis was performed by one investigator without knowledge of group affiliation or perinatal history. This analysis included the removal of nonbrain tissue and the creation of a WM skeleton based on the fractional anisotropy (FA) data of all infants aligned to a common space using nonlinear registration. The mean FA image was created to form a mean FA skeleton representing the centers of all tracts common for the sample. The skeleton was thresholded at FA >0.2 and included 52,688 mm^3 voxels. The threshold of 0.2 was chosen by visual inspection of the WM skeleton to include all major WM tracts. To reduce multiple comparisons in a small sample study, MD was used as the metric of interest rather than FA, as it has been shown to be less affected by motion artifacts in pediatric groups [15]. The invariant tract skeleton for each participant was used to test for differences in white matter MD values.

Statistics

Based on the proportion of postnatal growth-restricted infants seen in Norway [16], a sample size of 120 infants per group was required to achieve 80% power with a p value <0.05 to detect a reduction of infants discharged as growth restricted from 60 to 40% [12]. To evaluate the differences between groups we used a Student's t test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables. The Mann-Whitney U test was used for variables not normally distributed. Linear regression analysis was used to adjust for selected variables providing adjusted marginal means of MD values. Voxel-based statistical analyses of MD data were carried out using permutation- and tract-based spatial statistics. Significance was assumed for p values <0.05, corrected for multiple comparisons and displayed as a color-coded overlay.

Results

Before DTI and after the enrollment of 50 participants a preplanned safety analysis was performed. A significantly higher occurrence of late-onset septicemia was observed in the intervention group, hence the research group decided to stop further inclusion of participants [13].

Nutrition and growth data were calculated based on 44 of the enrolled 50 VLBW infants (total sample). Mean (in $weeks^{days}$) gestational age at birth was 28^2 weeks (standard deviation, SD = 2.4 weeks) and mean BW was 1,013 g (SD = 246 g). Interpretable DTI images were available from 25 infants (DTI sample; fig. 1): mean gestational age at birth was 28^2 weeks (SD = 2.4 weeks) and mean BW was 1,035 g (SD = 248 g).

No differences regarding serious clinical outcomes or mortality were detected between the total and DTI sample, except for late-onset septicemia in the total sample (table 1) [13]. A significantly lower BW among infants in the intervention groups was observed. Growth velocity was significantly higher and similar to intrauterine growth rates (16–17 g/kg/day) [14, 17] in both the total and DTI samples (table 1). We observed a significantly higher z score change in head circumference in the total sample but not in the DTI sample. However, among infants with DTI scans the mean z score change was positive in the intervention group (0.24) and negative in the control group (–0.12), suggesting improved head circumference growth. Growth velocity, weight when DTI was performed and the z score change in head circumference indicate improved growth among the intervention VLBW infants in both the total and DTI samples.

Mean PMA of the 25 infants with DTI images was 43^3 weeks (SD = 1.6 weeks, range 41^6–47^4) when scanned. Mean PMA (n = 14) was 43^5 weeks (SD = 1.7 weeks, range 42^1–47^4) among infants in the intervention group and 43 weeks (SD = 1.4 weeks, range 41^6–46^5) in the control group (n = 11). Scanning time was approximately 30 min and no adverse incidents occurred. Voxel-based analyses

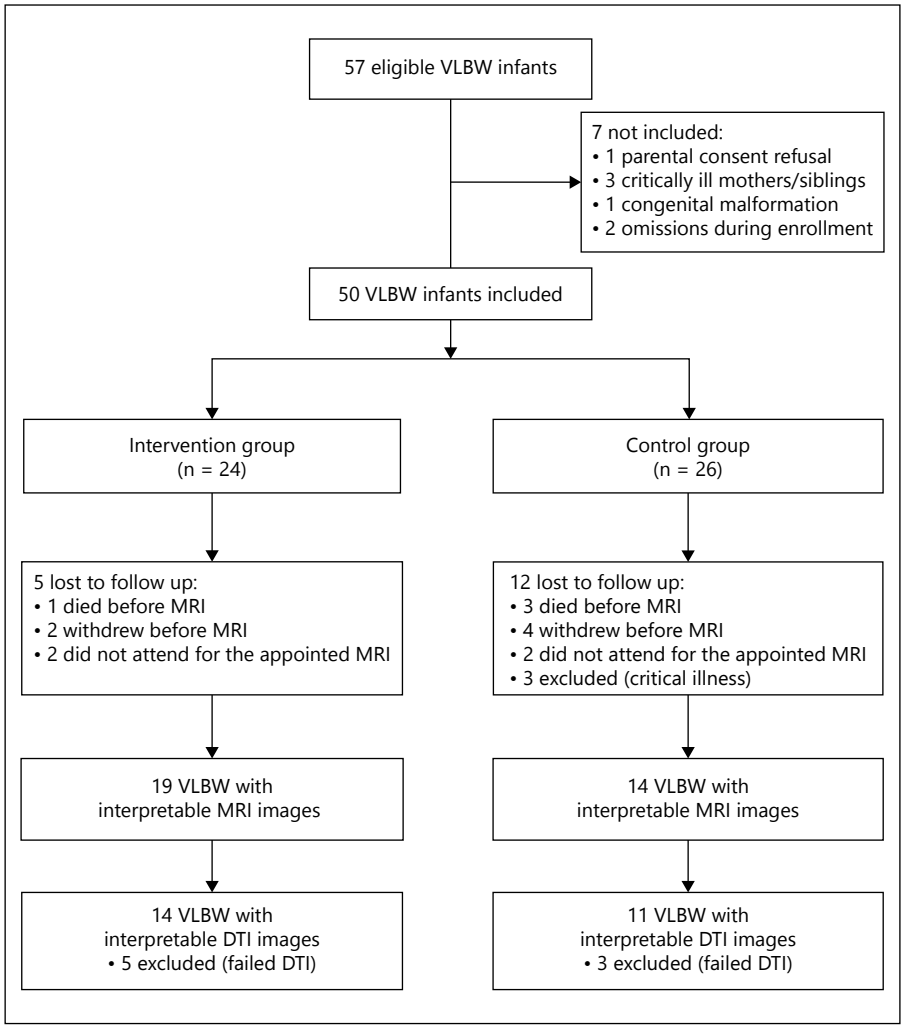

Fig. 1. Flowchart. Some infants failed DTI due to movement artifacts.

throughout the WM skeleton showed significantly lower MD values in the cingulum, corticospinal tract, superior longitudinal fasciculi (SLF) and uncinate fasciculi (table 2) among infants in the intervention group. No significant differences in MD were observed between the sexes. MD values remained significantly lower in the SLF (table 2; fig. 2), when adjusting for BW and age when scanned.

Discussion

This study evaluated the relationship between enhanced nutrient supply, growth and maturation of cerebral connective tracts analyzed using DTI close to term-equivalent age in VLBW infants. Infants on the enhanced nutrient supply demonstrated increased growth velocity and similar to normal intrauterine growth [12, 14, 17]. In addition, improved head circumference growth was observed, with a positive mean z score change of 0.24 compared to a negative change of –0.12 in the control group.

DTI examination revealed significantly lower MD in large regions of the cerebral WM tracts, especially the SLF. The SLF involves motor behavior, perception and language. The SLF has shown altered diffusivity in preterm born children where diffusivity characteristics have been shown to be involved in cognitive control [18]. Microstructural differences in connective tracts may underlie some of the cognitive and behavioral difficulties seen among preterm born infants and efforts should be made to prevent WM injury. Ghods et al. [19] demonstrated a positive correlation between head circumference growth and neurodevelopmental outcome. Normal antenatal

Table 1. Clinical outcomes and selected characteristics

	Total sample (n = 44)			Infants with DTI (n = 25)		
	intervention (n = 23)	control (n = 21)	p value	intervention (n = 14)	control (n = 11)	p value
Mean gestational age at birth, weeks[days]	28[1] (25–33[4])	28[3] (24–32[4])	0.66	27[4] (25–33[4])	29[1] (24–32[4])	0.12
95% CI	27–29[2]	27[3]–29[4]		26[1]–29	27[5]–30[4]	
Mean birth weight, g	936 (460–1,311)	1,097 (571–1,414)	0.03	932 (460–1,244)	1,166 (571–1,414)	0.02
95% CI	839–1,032	986–1,209		810–1,054	1,007–1,325	
Small for gestational age, n	11 (48)	4 (19)	0.04	5 (36)	2 (18)	0.41
Sex (male), n	14 (61)	14 (67)	0.69	10 (71)	6 (55)	0.43
Late onset septicemia, n	14 (61)	6 (29)	0.04	9 (64)	3 (27)	0.07
Bronchopulmonary disease, n	5 (22)	5 (24)	0.87	3 (21)	1 (9)	0.60
Retinopathy of prematurity (severe grade III/+ disease), n	3 (13)	1 (5)	0.61	3 (21)	0 (0)	0.23
Intraventricular hemorrhage[a] (grade ≥3), n	2 (9)	2 (10)	0.92	2 (14)	0 (0)	0.49
Necrotizing enterocolitis, n	1 (4)	1 (5)	0.95	1 (7)	0 (0)	0.99
Periventricular leukomalacia[a] (grade ≥3), n	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Median growth velocity[b], g/kg/day	17.4	13.8	<0.001	16.5	13.8	0.01
IQR	2.49	2.36		3.68	2.79	
Mean weight when DTI was performed, g	–	–	–	4,289±664	3,752±562	0.04
95% CI	–	–	–	3,906–4,673	3,374–4,130	
Mean head circumference at birth, cm	25.5±1.96	26.6±2.29	0.09	25.4±2.18	27.3±2.0	0.04
95% CI	24.6–26.3	25.6–27.6		24.2–26.7	25.9–28.6	
Mean head circumference at 36 weeks' PMA, cm	33.4±1.50[c]	32.5±1.41	0.06	33.2±1.67[c]	33.0±1.19	0.73
95% CI	32.7–34.0	31.9–33.2		32.2–34.2	32.2–33.8	
Mean △z score head circumference	0.63±0.65[c]	–0.25±0.58	<0.001	0.24±0.43[c]	–0.12±0.74	0.15
95% CI	0.34 to 0.92	–0.51 to 0.02		–0.02 to 0.50	–0.61 to 0.38	
Mean head circumference when DTI was performed, cm	–	–	–	38.2±1.52	38.0±1.27	0.76
95% CI	–	–	–	37.3–39.0	37.1–38.8	

Values in parentheses are ranges or percentages, as appropriate. CI = Confidence interval; IQR = interquartile range; △z score = z score change from birth. [a] Diagnosed with cranial ultrasound, prior to DTI. [b] From birth to 36 weeks' PMA. [c] 1 data set missing.

growth is associated with more mature WM and reduced MD is seen with improved postnatal development and maturation [20]. All observed effects were in the hypothesized direction, suggesting improved maturation of the cerebral connective tracts among infants receiving enhanced nutrition.

A balanced nutrient supply is essential for optimal growth and neurodevelopment in VLBW infants. Preterm infants are at increased risk of metabolic syndrome later in life. It is unclear as to what period has the most negative effect on blood pressure and metabolic health. Growth during later infancy and childhood appears to be a major promoter of later metabolic and cardiovascular disadvantages [21]. Early high protein supply, customized total parenteral nutrition and individualized fortified human milk may limit extrauterine growth restriction, promote growth and reduce the risk of developing metabolic syndrome. Recent research has shown no long-term advantages on intellectual or visual development among formula-fed preterm infants supplemented with long-chain polyunsaturated fatty acids [22]. However, breastfed term-born infants demonstrated increased WM development with cognitive and behavioral improvements [23], which may indicate that the content of breast milk is important for neural growth and WM development.

There are limitations to this study. Adverse neurodevelopment might be mediated by WM abnormalities seen in prematurely born infants with septicemia. A significantly higher number of VLBW infants with late-onset septicemia were observed among the infants in the intervention group in the total sample [13]. It is debatable whether rapid growth and electrolyte disturbances could cause an increased risk of septicemia [13]. Postnatal infection in preterm newborns is an important risk factor for abnormal brain development and WM abnormalities can predict cognitive outcomes [7, 24]. VLBW infants in the control group, with late onset septicemia,

Table 2. Mean MD values in selected brain regions

	Intervention group (n = 14)	Control group (n = 11)	p value
Crude analysis			
Cingulum, mm^2/s	1.19×10^{-3} (7.54×10^{-5})	1.27×10^{-3} (5.40×10^{-5})	0.01
95% CI	1.15×10^{-3}–1.23×10^{-3}	1.23×10^{-3}–1.30×10^{-3}	
Corticospinal tract, mm^2/s	1.08×10^{-3} (3.21×10^{-5})	1.11×10^{-3} (3.18×10^{-5})	0.02
95% CI	1.06×10^{-3}–1.10×10^{-3}	1.09×10^{-3}–1.13×10^{-3}	
SLF, mm^2/s	1.18×10^{-3} (6.18×10^{-5})	1.24×10^{-3} (5.70×10^{-5})	0.02
95% CI	1.15×10^{-3}–1.22×10^{-3}	1.21×10^{-3}–1.28×10^{-3}	
Uncinate fasciculus, mm^2/s	1.26×10^{-3} (5.88×10^{-5})	1.32×10^{-3} (7.15×10^{-5})	0.03
95% CI	1.23×10^{-3}–1.29×10^{-3}	1.27×10^{-3}–1.37×10^{-3}	
Adjusted for age when scanned[a]			
Cingulum, mm^2/s	1.19×10^{-3}	1.26×10^{-3}	0.02
95% CI	1.16×10^{-3}–1.23×10^{-3}	1.22×10^{-3}–1.30×10^{-3}	
Corticospinal tract, mm^2/s	1.08×10^{-3}	1.10×10^{-3}	0.05
95% CI	1.06×10^{-3}–1.10×10^{-3}	1.09×10^{-3}–1.12×10^{-3}	
SLF, mm^2/s	1.19×10^{-3}	1.24×10^{-3}	0.04
95% CI	1.16×10^{-3}–1.22×10^{-3}	1.20×10^{-3}–1.27×10^{-3}	
Uncinate fasciculus, mm^2/s	1.27×10^{-3}	1.31×10^{-3}	0.06
95% CI	1.24×10^{-3}–1.30×10^{-3}	1.28×10^{-3}–1.34×10^{-3}	
Adjusted for late-onset septicemia[a]			
Cingulum, mm^2/s	1.20×10^{-3}	1.26×10^{-3}	0.05
95% CI	1.16×10^{-3}–1.23×10^{-3}	1.21×10^{-3}–1.30×10^{-3}	
Corticospinal tract, mm^2/s	1.08×10^{-3}	1.11×10^{-3}	0.05
95% CI	1.06×10^{-3}–1.10×10^{-3}	1.09×10^{-3}–1.13×10^{-3}	
SLF, mm^2/s	1.19×10^{-3}	1.24×10^{-3}	0.05
95% CI	1.15×10^{-3}–1.22×10^{-3}	1.20×10^{-3}–1.28×10^{-3}	
Uncinate fasciculus, mm^2/s	1.26×10^{-3}	1.32×10^{-3}	0.08
95% CI	1.23×10^{-3}–1.30×10^{-3}	1.27×10^{-3}–1.36×10^{-3}	
Adjusted for BW and age when scanned[a]			
Cingulum, mm^2/s	1.20×10^{-3}	1.25×10^{-3}	0.08
95% CI	1.16×10^{-3}–1.24×10^{-3}	1.21×10^{-3}–1.30×10^{-3}	
Corticospinal tract, mm^2/s	1.08×10^{-3}	1.11×10^{-3}	0.05
95% CI	1.06×10^{-3}–1.10×10^{-3}	1.09×10^{-3}–1.13×10^{-3}	
SLF, mm^2/s	1.18×10^{-3}	1.24×10^{-3}	0.04
95% CI	1.15×10^{-3}–1.22×10^{-3}	1.20×10^{-3}–1.28×10^{-3}	
Uncinate fasciculus, mm^2/s	1.27×10^{-3}	1.31×10^{-3}	0.10
95% CI	1.24×10^{-3}–1.30×10^{-3}	1.27×10^{-3}–1.34×10^{-3}	

Values are means (with SD in parentheses) and 95% CI. CI = Confidence interval. [a] MD values are adjusted marginal means with 95% CI.

demonstrated increased MD values in several brain areas. This could reflect some brain abnormalities. However, an opposite trend was seen among VLBW infants in the intervention group with late-onset septicemia, suggesting that enhanced nutrient supply might modulate microstructural brain alterations caused by septicemia/prematurity. The latter data are not shown (nor whether infants with interpretable DTI results are comparable to those without), as care must be exerted when such conclusions are drawn due to the small sample size, low statistical power and wide range in PMA when the MRI was performed. The clinical investigators and parents were not blinded to group affiliation. However, the MRI examiner was blinded to group affiliation. Our study lacks a term-born control group and we cannot be sure if the nutrient intervention may normalize WM development.

Prematurely born infants are at increased risk of cognitive and behavioral shortcomings [1] and DTI may help associate WM phenotypes with cognitive development. A

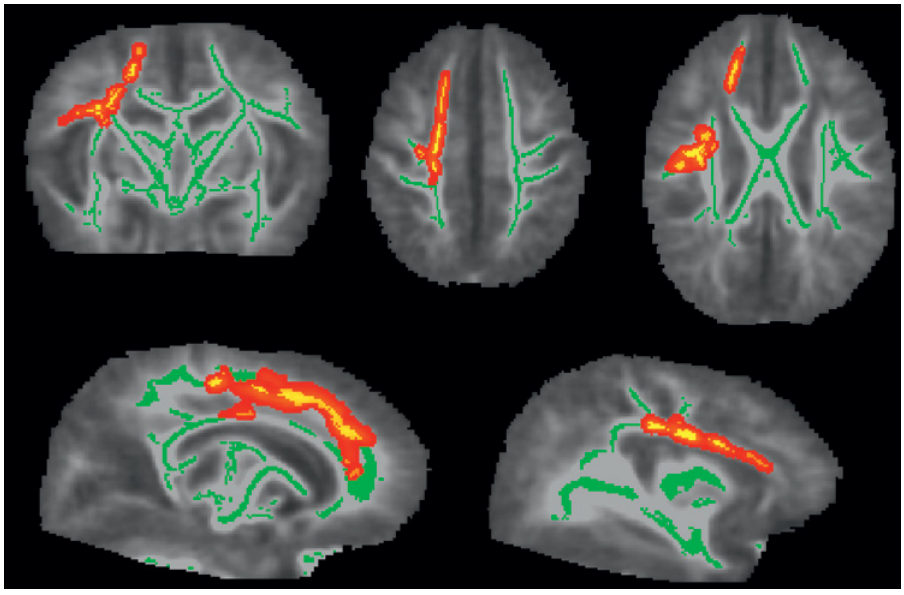

Fig. 2. Voxel-based DTI results in the SLF. The common WM skeleton (green) and mean FA volume are shown in a digitally processed image. The locus of the group effect, identified in voxel-wise comparisons of MD adjusted for BW and age when scanned, are shown in the SLF (yellow/red).

reduced MD in infants undergoing nutrition intervention may reflect maturation, axonal development or myelination compared to nonenriched controls, although the exact neurobiological correlates are not clear. The observed differences across prematurely born groups suggest that facilitation of WM development is possible with nutritional intervention. Enhanced nutrient supply to VLBW infants improved postnatal growth velocity, head circumference growth and maturation of cerebral connective tracts, the latter being evaluated using DTI. Studies with similar design, sufficient power and number of included participants are warranted.

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