Effects of a Multicomponent Lipid Emulsion on Brain Volumes in Extremely Low Birth Weight Infants

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Abstract

Objective During the early weeks of life optimization of nutrition in extremely preterm infants presents a critical opportunity to attenuate the adverse neurological consequences of prematurity and potentially improve neurodevelopmental outcome. We hypothesized that the use of multicomponent lipid emulsion (MLE) in parenteral nutrition (PN) would be related to larger volume of the cerebellum on brain magnetic resonance at term of equivalent age (TEA) in extremely low birth weight (ELBW) infants.

Study Design We analyzed the brain magnetic resonance imaging (MRI) at TEA of a cohort of preterm infants with gestational age $\leq$28 weeks and/or birth weight $<$1,000 g randomly assigned in our previous trial to receive an MLE or soybean-based lipid emulsion (SLE). The primary outcome of the study was the cerebellar volume (CeV), valued on MRI acquired at TEA. Secondary outcomes included total brain volume (TBV), supratentorial volume, brainstem volume, and CeV corrected for TBV evaluated on MRI acquired at TEA.

Results MRIs at TEA of 34 infants were then analyzed: 17 in the MLE group and 17 in the SLE group. The postmenstrual age (PMA) at which MRIs were performed were comparable between the two study groups. The CeV as well as the PMA-corrected CeV were significantly higher in the MLE group than in the SLE group. No difference was found among the other brain volumes considered.

Conclusion Our results suggest that the use of MLE in PN could promote CeV growth in ELBW infants, valued with MRI at TEA.

Keywords
- brain volume
- multicomponent lipid emulsion
- magnetic resonance imaging
- preterm infants

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Key Points

- Optimization of nutrition in extremely low birthweight infants.
- Use of multicomponent lipid emulsions in parenteral nutrition.
- Larger cerebellar volume with use of multicomponent lipid emulsion.

During the early weeks of life, developmental immaturity and clinical fragility of extremely preterm (EPT) infants limit oral and enteral feeding. Parenteral nutrition (PN) allows provision of energy requirements and essential nutrients, including fatty acids. The optimization of nutrition presents a critical opportunity to attenuate the adverse neurological consequences of prematurity and potentially to improve neurodevelopmental outcome.[1]

The last trimester of gestation is a critical period for brain growth and maturation; during this period, the cerebellum and cortical gray matter exhibit the highest growth rates, with 4- to 5-fold increase in volume.[2] Fat intake has been shown to have a large effect on brain growth.[3]

For many years soybean-based lipid emulsion (SLE) has been the principal source of intravenous fat. SLE is rich in omega-6 (ω-6) polyunsaturated fatty acids (PUFAs), with minimal omega-3 (ω-3) PUFAs. In the last decade, newer lipid emulsions (LEs) have been introduced to offer a more balanced provision of lipids derived from multiple sources. Multicomponent lipid emulsion (MLE) includes medium-chain triglycerides, which are rapidly metabolized lipids; soybean oil, which is a source of essential fatty acids; olive oil, which naturally contains the antioxidant vitamin E; and fish oil, rich of ω-3 PUFAs, which are known for their anti-inflammatory effects.

Fish oil has a higher ratio of ω-3 to ω-6, as compared with soybean oil, especially because of the high content of ω-3 long-chain PUFAs, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid, which seem to be crucial for growth of preterm infants.[4–8]

In our previous study, we found that the use of MLE (SMOFlipid 20%, Fresenius Kabi, Italy) in very low birth weight (VLBW) infants significantly reduces the loss of head circumference (HC) and length *z*-scores from birth to 36 weeks' postmenstrual age (PMA) or at discharge home compared with the use of pure SLE (Intralipid 20%, Fresenius Kabi, Italy).[8]

We hypothesized that the use of MLE in PN would be related to larger volume of the cerebellum on brain magnetic resonance at term of equivalent age (TEA) in extremely low birth weight (ELBW) infants.

Materials and Methods

Study Design and Patients

We retrospectively analyzed the brain magnetic resonance imaging (MRI)—acquired at TEA—of a cohort of preterm infants with gestational age (GA) ≤28 weeks and/or birth weight (BW) <1,000 g, admitted to the Neonatal Intensive Care Unit of the Fondazione Policlinico Universitario Agostino Gemelli, IRCCS in Rome, Italy, between December 1, 2015, and May 31, 2019. The enrolled infants were a cohort of subjects randomly assigned in our previous trial to receive an MLE (SMOFlipid 20%, Fresenius Kabi, Italy) or SLE (Intralipid 20%, Fresenius Kabi, Italy).[8]

Infants with congenital or chromosomal malformations, inborn errors of metabolism, and/or congenital infections of the central nervous system, and with major brain pathology such as intraventricular hemorrhage (IVH)[9] grade 3 or higher, periventricular leukomalacia (PVL),[10] and/or parenchymal hemorrhagic infarction on cerebral ultrasound were excluded.

The study protocol was approved by Institutional Review Board (Prot. ID 2759). Written informed consent was obtained from the parents.

Data Collection

Baseline databased on sex, BW and BW *z*-score, HC and HC *z*-score, length and length *z*-score, GA (based on the last menstrual period, ultrasound in early pregnancy, and postnatal physical examination), the number of prenatal (two doses of intramuscular betamethasone 12 mg 24 h apart), and postnatal steroid course were recorded. Furthermore, BW, HC, length, and their *z*-scores at time of MRI scan were included.

The following clinical outcomes were recorded for each infant: respiratory distress syndrome; pharmacologically treated patent ductus arteriosus; bronchopulmonary dysplasia, diagnosed according to consensus definition[11] and only moderate and severe degrees were considered; necrotizing enterocolitis (NEC), diagnosed using modified Bell's criteria[12] and only degrees >2A were considered; any stage of retinopathy of prematurity[13]; late-onset sepsis, defined as a positive blood culture or suggestive clinical and laboratory findings leading to treatment with antibiotics for at least 7 days despite absence of a positive blood culture; and length of hospital stay.

Nutritional Intake

The composition of the two LEs are detailed in ►Table 1. Daily total parenteral and enteral protein, fat, and caloric intakes for the first 28 days of life were available for all infants.

Intravenous lipids were administered at a dose of 1.5 g/kg/d within first 24 hours of life and were gradually increased by 0.5 g/kg/d until the dose of 3 g/kg/d was reached within the first week of life. According to our local protocol, the parenteral lipid intake was reduced by 25 to 50% when plasma triglycerides concentrations were between 265 and 442 mg/dL and was stopped when they exceeded 442 mg/dL. The feeding protocol provided that a minimal enteral feeding was started on the first day of life. Enteral feeding was

Table 1 Composition of the multicomponent lipid emulsion and the pure soybean oil emulsion

Lipid emulsion	MLE (SMOF lipid)	SLE (Intralipid)
Oil source, %		100
Soybean	30	
Coconut (MCT)	30	
Olive	25	
Fish	15	
Composition of major fatty acids, %		
MCTs		
Caproic acid (6:0)	Trace	–
Caprylic acid (8:0)	17	–
Capric acid (10:0)	12	–
Lauric acid (12:0)	0.2	–
Long-chain triacylglycerols		
Myristic acid (14:0)	1	0.2
Palmitic acid (16:0)	9	11
Palmitoleic acid (16:1n-7)	2	–
Stearic acid (18:0)	3	4
Oleic acid (18:1n-9)	29	24
ω-6 long-chain triacylglycerols		
Linoleic acid (18:2n-6)	19	53
Arachidonic acid (20:4n-6)	0.5	–
ω-3 long-chain triacylglycerols		
α-Linolenic acid (18:3n-3)	2	8
Eicosapentaenoic acid (20:5n-3)	3	–
Docosahexaenoic acid (22:6n-3)	2	–
Phytosterols, mg/L	47.6	348
α-Tocopherol, mg/L	200	38

Abbreviations: MCT, medium-chain triacylglycerols; MLE, multicomponent lipid emulsion; SLE, soybean-based lipid emulsion.

increased by 20–30 mL/kg/d. All infants received human milk (own mother's milk or donor milk); human milk was enriched with fortifier (Aptamil BMF, Milupa, Germany) when enteral feeding of 100 mL/kg/d was reached.

Magnetic Resonance Imaging

All MRI investigations were performed according to a standard protocol on a 1.5 Tesla MRI system (Philips Healthcare) with a standard head coil.

Infants were sedated using Sevoflurane in O_2 and administered by vaporization or intravenous midazolam before the examination as the clinical local protocol.

Heart rate, transcutaneous oxygen saturation, and respiration rate were continuously monitored, and an expert anesthetist was present throughout the entire examination.

The scanning protocol included T2- and T1-weighted imaging. Parameters of the scanning protocol included: axial three-dimensional (3D) T1-weighted image, coronal 3D T1-weighted image, axial T2-weighted image, and coronal T2-weighted image.

We used axial T2-weighted MRI to measure supratentorial volume (SuV), cerebellar volume (CeV), brainstem volume (BsV), total brain volume (TBV), and CeV corrected for TBV.

SuV was defined as the volumes of the cerebral hemispheres, including cortical gray matter, basal ganglia, and white matter, without the lateral ventricles, the III ventricle, and the cerebrospinal fluid (CSF) spaces. BsV was defined as the volumes of the midbrain, pons, and medulla oblongata without the CSF spaces, the IV ventricle, and the Silvian acqueduct. CeV was defined as the volume of the entire cerebellum (vermis and hemispheres), without the CSF spaces and the IV ventricle. TBV was defined as the volume of all brain structures, that is, intracranial volume without the volume of the ventricles and CSF (►**Fig. 1**). All measures were corrected for PMA at the time of scan with linear regression analysis.

Measurements were performed twice, with an automatic segmentation method and then with a semiautomatic segmentation open-source program called ITK-SNAP (version

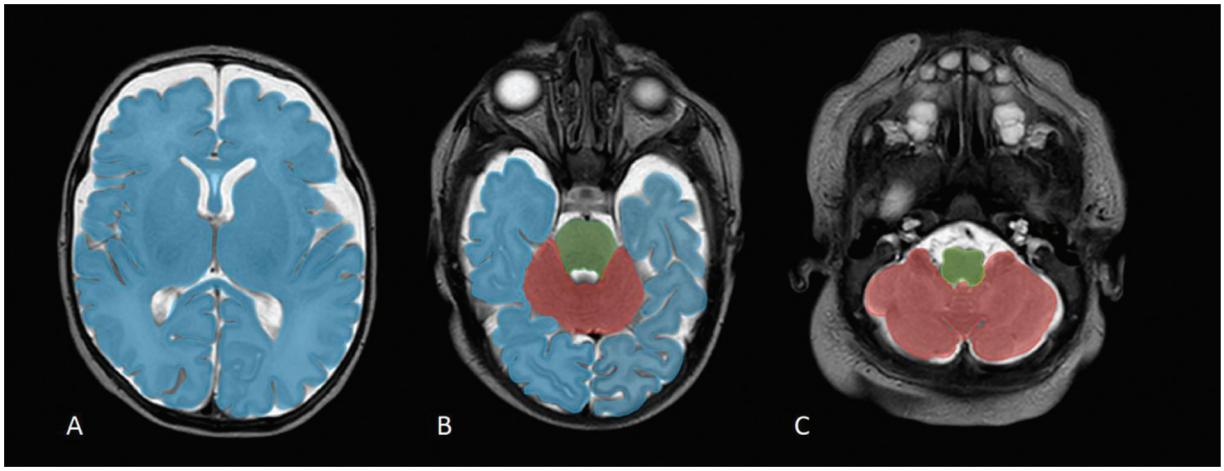

Fig. 1 Volumetric measurements, T2-weighted axial MR images. Supratentorial volume is shown in blue-shaded areas (**A**, **B**); cerebellar volume is shown in red-shaded areas (**B**, **C**); brainstem volume is shown in green-shaded areas (**B**, **C**).

3.8.0, University of Pennsylvania, Philadelphia, PA), using the Cavalieri's principle.[14,15]

Two neonatologists with experience in the field of neonatal neuroimaging (M.L.T. and C. Cocca) and a neuroradiologist (G.D.A.) evaluated the MRI scans for brain injury according to Kidokoro et al.[16]

Primary and Secondary Outcomes

The primary outcome of the study was the CeV valued on MRI acquired at TEA.

Secondary outcomes included TBV, SuV, BsV, and CeV corrected for TBV evaluated on MRI acquired at TEA.

Sample Size and Statistical Analyses

The sample size calculation was based on the literature data according to which premature infants with a mean GA of 28 weeks, and without severe IVH (grades 3–4), have a mean CeV measured with MRI equal to $18.3 \pm 3.2\ cm^3$.[17] Expecting an 18% gain in CeV (equal to $3.3\ cm^3$) in premature infants who received the MLE, a sample of at least 16 infants per arm is required, considered an α error of 0.05 and a study power of 80%.[18]

Data were analyzed with Statistical software SPSS for Windows version 25.0 (SPSS, Inc., Chicago, IL). Continuous variables are expressed as mean and standard deviation or as median and interquartile range, whereas categorical variables are expressed as numbers and percentages. Continuous variables were first tested for normal distribution by using the Shapiro–Wilk test. Categorical variables were compared using the chi-squared test or the Fisher's exact test. Continuous variables were compared using student *t*-test for independent samples (to compare data with normal distribution) or Mann–Whitney U test (to compare the others continuous data).

Because the volumes increase with PMA, we corrected the volume with linear regression analysis according to the following equation: corrected volume = measured volume + the slope × (40 − PMA on MRI). The level of significance was set at $p < 0.05$.

Results

In our institution, according to local care protocol, preterm infants with GA ≤ 28 weeks and/or BW <1,000 g, and those neonates with cerebral abnormalities at echography, regardless of GA and BW, underwent cerebral MRI. Then, 51 patients from the original trial were studied with MRI at TEA. Seventeen patients were excluded: 5 because of IVH > grade 2, 11 because of PVL, and 1 because of parental informed consent refusal. MRIs at TEA of 34 infants were then analyzed: 17 in the MLE group and17 in the SLE group (►Fig. 2).

No differences were observed between groups at baseline and for the main clinical outcomes (►Table 2). The mean PN and enteral nutrition intakes, including energy, protein, and lipid intake, were similar for both groups over the first 28 days of life. Moreover, there were no differences between the groups regarding the number of days required to reach full enteral feeding and the cumulative days of PN (►Table 3).

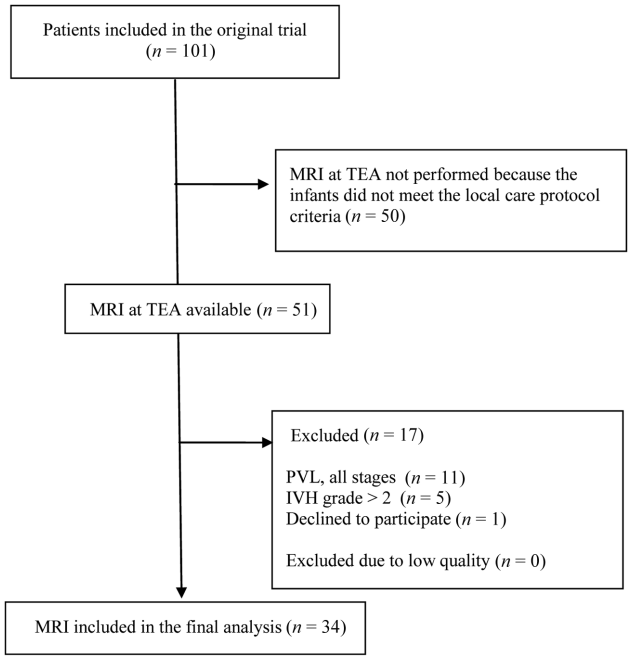

Fig. 2 Flowchart of included infants. IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; PVL, periventricular leukomalacia; TEA, term of equivalent age.

The PMA at which MRIs were performed were comparable between the two study groups. The CeV as well as the PMA-corrected CeV were significantly higher in the MLE group than in the SLE group. No difference was found among the other brain volumes considered, and also CeV corrected for TBV was similar between groups (►Table 4).

Discussion

In this retrospective study, we found that the use of MLE in PN positively influences the CeV in ELBW infants, valued with MRI at TEA. Our previous randomized controlled trial showed that the use of MLE in VLBW infants significantly reduces the loss of HC and length *z*-scores from birth to 36 weeks' PMA or at discharge home compared with the use of pure SLE.[8] MRI study at TEA of a cohort of ELBW infants randomized in this previous study confirms the beneficial effect of MLE on CeV. However, we could not confirm these results when we adjusted the CeV for TBV.

The biological plausibility of our finding is that the DHA, highly contained in the MLE, is a structural constituent of cellular membranes of the gray matter structures.[19,20] DHA are also involved in neurogenesis, antiapoptotic effects, and synaptic plasticity. EPT infants are generally born before the completion of normal placental transfer and DHA deposition in fetal tissue: MLE may contribute to restoring this DHA loss, thus helping brain development.

The ω-6 long chain polyunsaturated fatty acids (LCPUFA) arachidonic acid (AA) is another important component of MLE, that is known for its structural function in cell membranes, signaling, specific neuroprotective protein activation, and

Table 2 Demographics and clinical characteristics

	MLE ($n = 17$)	SLE ($n = 17$)	p
Gestational age (wk)	25.9 ± 1.8	27.0 ± 1.8	0.10
Male sex (*n*)	7 (41)	6 (35)	0.7
Birthweight (g)	665 (575–781)	735 (645–815)	0.26
Birthweight (*z*-score)	−0.38 ± 1.1	−0.42 ± 1.1	0.92
Length, cm	32.3 ± 2.5	33.5 ± 2.6	0.17
Length *z*-score	−0.35 ± 0.93	−0.24 ± 1.53	0.8
Head circumference (cm)	22.0 (21.0–24.1)	23.1 (21.5–25.3)	0.21
Head circumference *z*-score	−0.81 ± 0.84	−0.71 ± 1.06	0.76
Prenatal steroids (*n*)	7 (41)	8(47)	0.73
Postnatal steroids (*n*)	6 (35)	3 (18)	0.44
NEC > 2A (*n*)	1 (5.8)	0 (0)	1
PDA (*n*)	10 (59)	9 (53)	0.73
RDS (*n*)	17 (100)	17 (100)	1
BPD (moderate/severe; *n*)	7 (41)	5 (29)	0.47
ROP (all stages; *n*)	16 (94)	13 (76)	0.34
Treated ROP (*n*)	3 (18)	2 (12)	1
Sepsis (*n*)	10 (59)	10 (59)	1
Length of stay (d)	114 (99–177)	105 (64–124)	0.077
Weight at time of MRI (g)	2,020 (± 429)	1,925 (± 493)	0.52
Weight *z*-score at time of MRI	−1.5 (± 0.99)	−1.6 (± 0.98)	0.81
Length at time of MRI (cm)	42.8 (± 2.1)	42.0 (± 3.3)	0.41
Length *z*-score at time of MRI	−1.8 (± 0.87)	−1.9 (± 1)	0.74
Head circumference at time of MRI (cm)	30.5 (± 1.4)	29.6 (± 1.8)	0.14
Head circumference *z*-score at time of MRI	−1.7 (± 0.94)	−2 (± 0.95)	0.3

Abbreviations: BPD, bronchopulmonary dysplasia; MLE, multicomponent lipid emulsion; MRI, magnetic resonance imaging; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SLE, soybean-based lipid emulsion.
Note: Data are reported as mean (± standard deviation), median (interquartile range), and number (%).

Table 3 Nutritional data during the first 28 days of life

	MLE ($N = 17$)	SLE ($N = 17$)	p
Parenteral nutrition duration (d)	50.0 ± 29.5	44.0 ± 28.6	0.53
Time to full enteral feeding (d)	40 (34–52)	36 (28–59)	0.57
Total caloric intake (kcal/kg/d)	92.6 ± 9.6	93.3 ± 18	0.89
Total intravenous caloric intake (kcal/kg/d)	76.2 ± 12	66.7 ± 24	0.16
Total enteral caloric intake (kcal/kg/d)	18.8 ± 18	33.7 ± 0.4	0.11
Total protein intake (g/kg/d)	3.3 ± 0.4	3.4 ± 0.39	0.22
Total intravenous protein intake (g/kg/d)	2.8 ± 0.4	2.5 ± 0.9	0.3
Total enteral protein intake (g/kg/d)	0.6 ± 0.6	1.1 ± 1.1	0.1
Total lipid intake (g/kg/d)	3.1 ± 0.7	3.2 ± 1.2	0.65
Total intravenous lipid intake (g/kg/d)	2.2 ± 0.38	1.8 ± 0.7	0.14
Total enteral lipid intake (g/kg/d)	1.2 ± 1	1.8 ± 1.7	0.21

Abbreviations: MLE, multicomponent lipid emulsion; SLE, soybean-based lipid emulsion.
Note: Data are presented as mean (±standard deviation) or median (interquartile range).

Table 4 Study outcomes

	MLE ($N = 17$)	SLE ($N = 17$	p
Postmenstrual age at MRI study	43.5 ± 8	42.8 ± 10	0.8
Cerebellum volume (cm^3)	24.0 ± 9.6	18.2 ± 6.2	**0.045**
Cerebellum volume corrected for PMA (cm^3)	22.3 ± 6.5	16.9 ± 7.2	**0.027**
Cerebellar volume corrected for total brain volume (%)	5.1 (4.3–7.3)	5.1 (3.9–7.2)	0.87
Supratentorial volume (cm^3)	284.7 (253.8–407.9)	283.4 (233.1–297.8)	0.16
Supratentorial volume corrected for PMA (cm^3)	358.3 (179.0–396.8)	294.9 (191.5–345.8)	0.25
Brainstem volume (cm^3)	6.0 ± 0.9	5.3 ± 9.9	0.053
Brainstem volume corrected for PMA (cm^3)	5.7 ± 9.6	5.2 ± 1.1	0.11
Total brain volume (cm^3)	379.5 (208.6–419.6)	316.6 (211.6–364.7)	0.21

Abbreviations: MLE, multicomponent lipid emulsion; MRI, magnetic resonance imaging; PMA, postmenstrual age; SLE, soybean-based lipid emulsion.
Note: Data are reported as mean (± standard deviation), and median (interquartile range). Bold p-values are statistically significant.

formation of eicosanoids. Preterm infants are at risk for adverse neurodevelopmental outcome and rely on parenteral and enteral nutrition for proper DHA and AA intake.[21,22]

Our findings are consistent with those of Hortensius et al, who studied a cohort of infants derived from a randomized controlled trial evaluating the effect of two parenteral LEs. They measured serum DHA and AA levels during the first 28 days of life in patients who received MLE or olive oil–based LE. They found that serum DHA levels were positively associated with volumes of several brain structures in EPT infants at TEA, including cerebellum. No effect of AA levels on brain volumes was found.[23]

Existing studies demonstrated the beneficial effect of early lipid intake on preterm brain development using MRI study.[24–26] Schneider et al demonstrated a significant relationship between cumulative energy and lipid intake in the first 2 weeks of life and cerebellar, basal nuclei, and TBVs assessed with MRI studies at TEA.[24] Coviello et al demonstrated a significant positive association between cumulative lipid intake in the first 4 weeks of life and cerebellar, basal ganglia and thalamic volumes.[25] Ottolini et al found that early cumulative lipid intake in the first month of life is associated with significantly greater CeV at TEA in very premature infants, using MRI study.[26] Our study differs from previous ones because our results underlined that the quality, and not only the cumulative quantity, of the lipids administered with PN plays a role in the development of brain structures of preterm infants.

We failed to find differences in the volumes of the other considered brain structures; this is not surprising because the sample size was calculated on the volume of the cerebellum, which shows the highest growth rate compared with other intracranial structures during the last trimester of pregnancy.[27,28] For this reason, while a small sample size allowed us to detect the growth differences of the cerebellum, which experiences a 34-fold increase in volume during this time period under favorable conditions, the small sample size may have contributed to not detecting differences between the other brains volumes. Cerebellum growth can, however, be considered a proxy for overall brain development, because cerebellum seems to play an essential role not only in sensorimotor and vestibular control, but also in cognition, emotion, and autonomic function.[29,30]

It is well known that adequate nutrition plays a crucial role for optimal brain growth and maturation.[31,32] Lipids and energy contributed most to the beneficial effect of nutrition, considering that lipids provided a third of total energy. Lipids are essential for brain development and participate in neuronal membrane structure formation and myelin synthesis.[33,34] Also, the optimization of protein and energy intake in the neonatal period has a positive impact on cognition, with effects persisting until adolescence.[35] Our findings suggest that the quality of nutrients composition may play a critical role for the brain development, at least for the cerebellum.

Strengths and Limitations

The strength of this study is that, despite its retrospective design, the cohort of infants derived from a randomized and controlled population, partially limiting the possibility of confounding factors. On the other hand, the small sample size is the major limitation of this study, reducing the possibility of statistically exploring whether other variables could have had an effect on CeV.

Conclusion

Our results suggest that the use of MLE in PN could promote CeV growth in ELBW infants, valued with MRI at TEA. While encouraging, our findings deserve to be confirmed on larger samples, as well as complemented by a neurological follow-up to assess whether the better neuroimaging data also correspond to better neurodevelopmental outcomes. For the original trial, which included the cohort of this study, a neurological follow-up was planned at 24 months of corrected age. The results of the 24-month follow-up will provide data on the possible role of LEs quality on neurodevelopmental outcome.

Authors' Contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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None.

Conflict of Interest

None declared.

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