Impact of Early Nutritional Intake on Preterm Brain: A Magnetic Resonance Imaging Study

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Objectives To investigate the association between early nutritional intake and brain development assessed by magnetic resonance imaging (MRI).

Study design A cohort of neonates born at ≤30 weeks gestational age underwent MRI at term equivalent age. Brain maturation and injury were assessed using the Kidokoro score. Two groups were defined by severity of the scores. The associations between macronutrients intake during the first 2 weeks of life, clinical factors, and imaging scores were analyzed using logistic regression.

Results MRI scores from group 1 patients (n = 27) were normal to mildly abnormal (0-5). Group 2 (n = 15) had more abnormal scores (6-12). The median gestational ages (IQR) were 27.4 (1.9) weeks in group 1 and 27.0 (2.9) weeks in group 2, with birth weights of 900 (318) g (group 1) and 844 (293) g (group 2). In group 2, energy, lipid, and carbohydrate intake were significantly lower than in group 1. Group 2 also showed higher rates of sepsis and clinical risk scores than group 1. After adjustments in bivariate models, higher energy and lipid intake remained significantly associated with improved scores on MRI. This association was stronger for the gray matter component of the score.

Conclusions Higher energy and lipid intake during the first 2 weeks after birth was associated with a lower incidence of brain lesions and dysmaturation at term equivalent age in preterm neonates. *(J Pediatr 2017;181:29-36).*

Given the rise in rates of preterm birth and survival, it is important to attempt to decrease rates of neurologic sequelae that may affect up to 40% of very preterm infants.[1,2] Optimizing early nutritional support has been shown to improve neurodevelopment in preterm infants.[3-6] During the first 2 weeks after birth, preterm infants are vulnerable to nutritional deficits.[3,4,7] Cumulative energy, protein, and lipid intakes have been correlated positively with cognitive and motor outcomes, even if their relative impacts are not fully clarified.[3-5] The effects of specific nutrients on brain lesions or morphologic maturation itself are also poorly understood. Further investigation is required to unravel proposed neuroprotective effects of nutrition in preterm infants.[8-10]

In the last decade, cerebral magnetic resonance imaging (MRI), and particularly newly developed techniques of MRI, have become powerful tools to assess preterm brain development.[10-13] MRI studies reveal that the preterm brain, even without severe injuries, may show "dysmaturation" that can lead to neurologic impairments later in life.[14-16] However, only a few MRI studies have investigated the effects of nutritional factors on brain morphology.[17-19] Isaacs et al[19] first observed larger caudate volumes, related to higher verbal IQ, in 38 ex-preterm male adolescents, who had been randomized to receive a high nutrient diet.[19] More recently, improved head growth and decreased regional white matter (WM) diffusivity at term equivalent age (TEA) were reported in 14 very low birth weight (BW) infants who received enhanced parenteral and enteral nutrition, suggesting nutritional improvements led to better WM maturation.[18] In contrast, brain volumes were not related to macronutrients in 2 observational studies.[17,20] However, these studies focused on particular brain structures and did not assess early nutritional impact.

The aim of our study was to investigate the association between morphologic brain development, assessed by MRI at TEA, and macronutrient and energy intakes during the first 2 weeks after birth. We used a semiquantitative MRI score,

BW	Birth weight
BPD	Bronchopulmonary dysplasia
CRIB	Critical risk index for babies
DOL	Day of life
GA	Gestational age
GM	Gray matter
MRI	Magnetic resonance imaging
TEA	Term equivalent age
WM	White matter

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described by Kidokoro et al[11] based on whole gray and WM growth, maturation, and lesion assessment.

Methods

The present study was nested in a prospective cohort that has been previously published.[13] It included 51 neonates born at less than 30 weeks of gestational age (GA) between February 2011 and May 2013 in the level III neonatal intensive care unit of the University Hospital of Lausanne, Switzerland. Exclusion criteria were parental refusal, major congenital malformations, severe cardiorespiratory instability, and/or intraventricular hemorrhage grade >II diagnosed by cerebral ultrasound before day of life (DOL) 5. Patients with missing nutritional information and those who dropped out of the study before TEA were excluded from the final analysis (**Figure 1**; available at www.jpeds.com). The study protocol was approved by the local ethics committee, and written parental informed consent was obtained.

MRI Examination, Analysis, and Data

MRI was performed on a 3-Tesla MAGNETOM Trio system (Siemens Healthcare, Erlangen, Germany), using a neonatal MRI-compatible incubator (Nomag; Lammers Medical Technology, Luebeck, Germany) with integrated neonatal head coil. The MRI-protocol included the following sequences (in-plane resolution, section thickness, repetition time, echo time, field-of-view): (1) inversion recovery T1-weighted turbo-spin-echo axial (0.6 mm, 3 mm with 10% gap, 8000 ms, 17 ms, 160 mm); (2) T2-weighted turbo-spin-echo axial (0.2 mm, 2.5 mm with 10% gap, 4520 ms, 143 ms, 160 mm); (3) T2-weighted turbo-spin-echo coronal (0.4 mm, 1.2 mm with 10% gap, 5410 ms, 159 ms, 200 mm); (4) T2* weighted gradient echo sequence (0.6 mm, 3 mm, 482 ms, 20 ms, 160 mm); and (5) magnetization-prepared dual rapid acquisition of gradient echo (MP2RAGE) (0.7 mm, 1.2 mm, 4000 ms, 3.17 ms, 190 mm, inversion time (TI) 1: 900 ms, TI 2: 2200 ms).

Brain maturation and injuries were assessed using the Kidokoro score.[11] This semiquantitative total score consists of 4 underscores (with a total of 13 scoring items, of which 6 are quantitative [brain metrics]): WM, cortex, deep gray matter (GM), and cerebellum. The last 3 underscores are summarized under GM score (7 items in total), whereas the WM abnormalities are summarized as WM score (6 items). The total score ranges from 0 to 40. The scores were assessed by 2 neonatologists trained in MRI reading (J.S., A.T.), blinded for patient's information and supervised by a neuroradiologist (P.Ha.) in case of disagreement.

Nutritional Data Collection and Calculation

During the study, parenteral and enteral nutrients were individualized daily, according to our nutritional protocol, based on the European Society for Paediatric Gastroenterology Hepatology and Nutrition recommendations.[21,22]

Carbohydrates and amino acids (Aminoven Infant 10%; Fresenius-Kabi AG, Oberdorf, Switzerland) were provided from birth at 5 mg/kg/minute and 1.5 g/kg/day, respectively. A lipid emulsion of soybean (Lipovenös 20%; Fresenius-Kabi AG) was added from DOL 3, at 0.5 g/kg/day until December 2011; from January 2012, a mixture of soybean and olive oil (Clinoleic 20%; Baxter AG, Volketswil, Switzerland) was introduced from DOL 2 at 1 g/kg/day. Daily progression was 1-2 mg/kg/minute for glucose (maximum 12 mg/kg/minute); 0.5 g/kg/day for amino acids (maximum 3.5 g/kg/day); and 0.5-1 g/kg/day for lipids (maximum 3-3.5 g/kg/day). Parenteral nutrition was weaned when enteral intake reached 120 ± 20 mL/kg/day.

Discontinuous milk feedings were initiated from DOL 1, at 15 ± 5 mL/kg/day and increased daily by 15 ± 5 mL/kg/day according to the enteral tolerance until 160 mL/kg/day were reached. When available, mother's own milk (fresh or frozen) was preferred; a preterm formula was otherwise provided (BEBA Alprem or BEBA Aliment pour Prématurés Etape 1; Nestlé, Vevey, Switzerland). Fortification (Aptamil Frauen-Milch-Supplement 4%; Milupa SA, Domdidier, Switzerland) was introduced when 100 mL/kg/day of human milk was tolerated.

Actual parenteral and enteral intakes were recorded in the electronic medical charts (Metavision; iMDsoft, Düsseldorf, Germany), allowing an exact record of enteral and parenteral intakes. Daily intake was summed from DOL 1 to 14 into a cumulative intake. Total intake was obtained adding enteral and parenteral contributions. Caloric intake calculations assumed that protein and carbohydrates provide 4 Kcal per g, and lipids provide 9 Kcal per g. Nutrient composition of human milk was calculated according to the American Academy of Pediatrics,[23] and the composition of formulas was calculated according to the manufacturer's declarations.

Clinical data were prospectively collected. Respiratory distress syndrome was defined as requiring exogenous surfactant; bronchopulmonary dysplasia (BPD) as ventilatory or supplementary oxygen requirement at the age of 36 weeks postmenstrual age; necrotizing enterocolitis as Bell stage ≥2; and sepsis as clinical signs of infection with positive blood culture and/or inflammatory syndrome. Intraventricular hemorrhage was graded according to Papile et al.[24] A BW small for GA was determined by a weight more than 2 SDs below the mean on the Fenton growth chart.[25] Weight gain (in g/kg/day) calculation was {1000 × (weight at TEA MRI−BW)/[(weight at TEA MRI + BW)/2]/number of days}.[26,27]

Statistical Analyses

Continuous variables were summarized by their median and IQR, and categorical variables were summarized by their frequency. Using the Kidokoro score on the TEA MRI, the study patients were divided into 2 groups: group 1, consisting of the patients with total Kidokoro scores <75 percentile (the reference group), and group 2, consisting of the patients with total scores ≥75th percentile (more severe abnormalities). Logistic regression analyses assessed associations between the 2 groups, nutritional intake, GA, BW, sepsis, sex, small for GA status, and comorbidities. The association between each nutrient and the outcome was adjusted on the covariable with a P value of <.05 in univariate analysis or other potential confounders. Statistical analysis was performed using Stata software v 14 (StataCorp, College Station, Texas).