Breast Milk Feeding, Brain Development, and Neurocognitive Outcomes: A 7-Year Longitudinal Study in Infants Born at Less Than 30 Weeks' Gestation

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Objectives To determine the associations of breast milk intake after birth with neurological outcomes at term equivalent and 7 years of age in very preterm infants

Study design We studied 180 infants born at <30 weeks' gestation or <1250 grams birth weight enrolled in the Victorian Infant Brain Studies cohort from 2001-2003. We calculated the number of days on which infants received >50% of enteral intake as breast milk from 0-28 days of life. Outcomes included brain volumes measured by magnetic resonance imaging at term equivalent and 7 years of age, and cognitive (IQ, reading, mathematics, attention, working memory, language, visual perception) and motor testing at 7 years of age. We adjusted for age, sex, social risk, and neonatal illness in linear regression.

Results A greater number of days on which infants received >50% breast milk was associated with greater deep nuclear gray matter volume at term equivalent age (0.15 cc/d; 95% CI, 0.05-0.25); and with better performance at age 7 years of age on IQ (0.5 points/d; 95% CI, 0.2-0.8), mathematics (0.5; 95% CI, 0.1-0.9), working memory (0.5; 95% CI, 0.1-0.9), and motor function (0.1; 95% CI, 0.0-0.2) tests. No differences in regional brain volumes at 7 years of age in relation to breast milk intake were observed.

Conclusion Predominant breast milk feeding in the first 28 days of life was associated with a greater deep nuclear gray matter volume at term equivalent age and better IQ, academic achievement, working memory, and motor function at 7 years of age in very preterm infants. *(J Pediatr 2016;177:133-9).*

In healthy, full-term populations, breastfeeding seems to be beneficial to neurodevelopment.[1-3] One proposed mechanism linking breastfeeding with brain development is the effect of specific nutrients in breast milk that are either absent from or present in lower amounts in infant formula.[4] Another potential mechanism is through greater sensitivity to the infant shown by mothers who provide breast milk,[5] because maternal sensitivity is associated with better neurodevelopment.[6] Connections between breastfeeding and infant development may also be explained in part by shared social determinants such as maternal education and family income, and maternal IQ.[7]

The effects of breast milk and breastfeeding on neurodevelopment may be quite different in very preterm infants than in those born at full term. Nutritionally, breast milk is considered the optimal food for full term infants, but preterm infants require fortification to match third trimester nutrient accretion rates.[8] Even with fortification, weight gain of breast milk-fed infants lags behind that of infants fed preterm formula,[9,10] suggesting possible undernutrition. In hospitalized very preterm infants, feedings are typically given via tube rather than directly at the breast, thereby uncoupling the ingestion of breast milk from the maternal interactions that occur during the act of breastfeeding. However, the time invested in expressing and delivering breast milk may reflect different levels of attachment or sensitivity. Given these differences between preterm and term infants, focused research is needed to evaluate the potential benefits of breast milk intake on the neurodevelopment of very preterm infants.

Direct imaging of the brain may shed light on mechanisms linking breast milk, brain growth, and neurodevelopment. In full-term infants, magnetic resonance imaging (MRI) of the brain demonstrated greater white matter development from 10 months to 4 years of age[11] and at 8 years of age[12]; and greater cortical thickness in adolescence[13] in relation to early breastfeeding exposure. In preterm infants,

MRI Magnetic resonance imaging

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one small study[14] (n = 50) found positive correlations of breast milk intake with total brain volume at 15 years of age. Another study[15] of preterm infants reported that greater breast milk intake was associated with improved corpus callosum maturation at term equivalent age (40 weeks postmenstrual age), but infants were not followed beyond neonatal discharge. Additional research is needed to determine the extent to which breast milk intake during the neonatal period affects the preterm infant brain and whether effects persist beyond the newborn period.

Our aims in this study were to examine associations of breast milk intake during the neonatal hospitalization with brain MRI characteristics at term equivalent and 7 years of age and neurodevelopmental outcomes at 2 and 7 years of age.

Methods

We studied participants in the Victorian Infant Brain Studies longitudinal cohort. Two hundred twenty-four infants born at <30 weeks' gestation or <1250 grams birth weight were enrolled before term equivalent age at the Royal Women's Hospital in Melbourne, Australia between July 2001 and December 2003. Exclusion criteria included congenital anomalies likely to affect brain development or function. Parents provided informed consent for their children to participate.

The Royal Women's Hospital and Royal Children's Hospital institutional review boards approved the study. For this analysis, we excluded 44 participants owing to missing breast milk data. The remaining 180 participants had available data for ≥1 outcome (n = 160 with term equivalent brain MRI; n = 173 with 2-year Bayley testing; n = 108 with 7-year brain MRI; and n = 161 with 7-year neurocognitive testing) and were included in the present analysis.

Breast Milk Intake

Study staff abstracted the daily volume of breast milk and formula intake for the first 28 days of life from the medical record. We focused on breast milk intake in the first 28 days with the goal of minimizing attrition owing to early transfer or discharge that could bias results. In a subset of 20 randomly selected participants, we abstracted data on breast milk intake (mL/kg/d) through day 40, and found a strong correlation with intake from birth to 28 days (Pearson $r = 0.95$). Breast milk was fortified according to unit-based practice. Preterm formula was used when a mother's own breast milk was unavailable or in short supply; donor breast milk was not used.

Brain MRI at Term Equivalent and 7 Years of Age

At term equivalent age (range, 3-42 weeks postmenstrual age), participants underwent brain MRI in a 1.5-T General Electric scanner (Signa Echospeed System; Milwaukee, Wisconsin). Infants were fed, swaddled, and placed in a supportive beanbag. No analgesia or sedation was given. T_1 and T_2/proton density-weighted images were acquired.[16] Structural images were semi-automatically segmented into white matter (unmyelinated, myelinated), cortical gray matter, deep nuclear gray matter (including basal ganglia and thalamus), and cerebrospinal fluid.[17,18] Hippocampi and cerebella were traced manually.[19,20]

At 7 years of age (range, 6.6-8.1), participants again underwent brain MRI. Children were scanned on a 3-esla Siemens Magnetom Trio scanner, with T_1-weighted images acquired (0.85 mm sagittal slices, flip angle = 9°, repetition time = 1900 ms, echo time = 2.27 ms, field of view = 210 × 210 mm, matrix = 256 × 256). Brain volumes were obtained using FreeSurfer, an automated imaging processing package (stable release version 4.4.0, http://surfer.nmr.mgh.harvard.edu), with manual editing as required. Cortical and cerebellar gray and white matter, and deep nuclear gray matter (thalamus, nucleus accumbens, caudate, putamen, pallidum) were estimated and volumes combined from both hemispheres. Cerebellar volume was calculated as the total cerebellar white plus gray matter. Total brain volume was the combined volumes of all brain structures. Hippocampi were traced manually.[21]

Neurodevelopmental Assessments at 2 and 7 Years of Age

Trained examiners administered the Bayley Scales of Infant Development, 2nd edition (Bayley-2) when children were 2 years of corrected age. The Bayley-2 comprises the Mental Development Index, which measures cognition, and the Psychomotor Development Index, which measures motor skills. Domains tested at 7 years of age included general intelligence (Wechsler Abbreviated Scale of Intelligence),[22] academic achievement (Word Reading and Math Computation subtests of the Wide Range Achievement Test),[23] attention (score subtest of the Test of Every Day Attention for Children),[24] working memory (Backward Digit Recall subtests of the Working Memory Test Battery for Children),[25] language (Core Language Index from the Clinical Evaluation of Language Fundamentals),[26] visual perception (Visual Closure subtest of the Test of Visual Perceptual Skills),[27] and motor function (Movement Assessment Battery for Children).[28] Higher scores on all of these measures indicate better performance. Scores from the Bayley-2, Wechsler Abbreviated Scale of Intelligence, Wide Range Achievement Test, Working Memory Test Battery for Children, and Clinical Evaluation of Language Fundamentals were age-standardized to a mean of 100 and SD of 15; the remaining tests were standardized to a mean of 10 (SD 3). We used corrected age for all scores. On the Bayley-2, children who fell below the basal threshold for testing were assigned a score of 45; children too impaired for testing were assigned a score of 40.

Covariates included infant sex, gestational age, exposure to antenatal or postnatal corticosteroids, supplemental oxygen requirement at 36 weeks, and diagnosis of sepsis or necrotizing enterocolitis were abstracted from the medical record. The Clinical Risk Index for Babies score is an illness severity indicator.[29] We calculated a social risk score comprising maternal age, parent marital status, education level of baby's primary caregiver, employment status and income of primary income earner, and language spoken at home.[30] Participants were categorized as being of lower (score, 0 or 1) or higher (score, ≥2) social risk. Using infant weight obtained with a digital scale at birth and