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Human milk and preterm infant brain development: A narrative review

Mandy Brown Belfort, MD MPH, **Terrie E. Inder, MBChB, MD**

Department of Pediatric Newborn Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Structured Abstract

Purpose.—To review and synthesize the literature on human milk and structural brain development and injury in preterm infants, focusing on the application of quantitative brain magnetic resonance imaging (MRI) in this field.

Methods.—Narrative review of the literature published from 1990 to 2021, indexed in PubMed, and reporting observational or interventional studies of maternal milk or donor milk in relation to brain development and/or injury in preterm infants, assessed with quantitative MRI at term equivalent age. Studies were characterized with respect to key aspects of study design, milk exposure definition, and MRI outcomes.

Findings.—We identified seven relevant studies, all of which were observational in design and published between 2013 and 2021. Included preterm infants were born at or below 33 weeks' gestation. Sample sizes ranged from 22 to 377 infants. Exposure to human milk included both maternal and donor milk. No study included a full-term comparison group. Main MRI outcome domains were: 1) white matter integrity, assessed with diffusion tensor imaging, resting state functional connectivity, or semi-automated segmentation of white matter abnormality and 2) total and regional brain volumes. Studies revealed that greater exposure to human milk vs. formula was associated with favorable outcomes, including: 1) more mature and connected cerebral white matter with less injury; and 2) larger regional brain volumes, notably in the deep nuclear gray matter, amygdala-hippocampus, and cerebellum. There was no consistent signature effect of human milk exposure, rather the beneficial associations were regional and tissue-specific neuroprotective effects on the areas of known vulnerability in the preterm infant.

Implications.—Evidence to date suggests that human milk may protect the preterm infant from the white matter injury and dysmaturation to which this population is vulnerable. Brain MRI at term equivalent age is emerging as a useful tool to investigate the effects of human milk on the preterm brain. When grounded in neurobiological knowledge about preterm brain injury and development, this approach holds promise for allowing further insight into the mechanisms

Address correspondence to: Dr. Mandy Brown Belfort, Brigham and Women's Hospital, Department of Pediatric Newborn Medicine, 221 Longwood Ave. BL-341, Boston, MA 02115, Phone: 617-525-4135, Fax: 617-525-4143.

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and pathways underlying beneficial associations of human milk with neurodevelopmental outcomes in this population, and in the investigation of specific milk bioactive components with neuroprotective or neurorestorative potential.

Introduction

Preterm infants are vulnerable to neurodevelopmental impairments in multiple domains including motor, cognitive, language, social-emotional, and executive functioning.[1] These vulnerabilities result from environmental exposures both before birth and within the neonatal intensive care unit (NICU) environment during a critical period in brain development. In this context, nutritional factors, including human milk, have been identified as protective.[2,3] For example, observational studies have consistently demonstrated that a higher dose of maternal milk in the NICU is associated with improved neurodevelopmental outcomes at preschool age and beyond.[4–7]

Several plausible mechanisms exist by which human milk may protect the preterm brain from injury and/or reduce the adverse effects of injury on development. First, nutrients such as docosahexaenoic acid (DHA) and choline are essential for normal brain development[8] and are present in human milk, but are not always added to preterm formula.[9,10] The milk fat globule membrane comprises a heterogeneous mixture of proteins, phospholipids, sphingolipids, gangliosides, choline, and sialic acid, nutrients that all play roles in early brain development and are lacking in preterm formula.[11] Second, mounting evidence points to direct, indirect, and interactive effects of myriad non-nutrient bioactive factors in human milk, such as lactoferrin, human milk oligosaccharides (HMOs), microbes, osteopontin, and milk exosomes.[12–18] Third, human milk provision may be a marker for greater parent presence and engagement in the NICU, as well as nurturing behaviors such as skin-to-skin care, which themselves predict increased human milk provision and drive better short- and long-term outcomes.[19,20]

In the past decade, quantitative brain magnetic resonance imaging (MRI) at term equivalent age has emerged as a powerful tool for defining in-vivo the brain injury and myriad disruptions in typical brain development that occur in the preterm infant, as well as for predicting long-term neurodevelopmental outcomes in this population.[21] MRI has also been used increasingly to uncover how nutritional exposures affect the developing preterm brain.[22,23] Similarly, MRI can be applied to address questions about how human milk feeding affects brain development in the NICU. Our aims were to 1) perform a narrative review of studies investigating relationships of human milk (maternal and/or donor) feeding in the NICU with quantitative brain MRI-derived measures at term equivalent age, and 2) consider this emerging literature in the context of existing knowledge about preterm brain injury and development during the period from birth to term equivalent age (“preterm period”), with implications for the investigation of novel, NICU-based clinical strategies to improve long-term outcomes.

Methods

We searched PubMed using the MeSH terms “human milk,” “infant, premature,” “magnetic resonance imaging,” and “brain.” This search strategy yielded 13 results. By reviewing article titles and abstracts for these 13 articles, we identified 5 articles meeting the following inclusion criteria: 1) observational or interventional design; 2) study of maternal milk or donor milk in relation to quantitative brain MRI outcome; 3) brain MRI performed near term equivalent age (40 weeks’ postmenstrual age); 4) participants were infants born preterm (<37 weeks). To identify additional articles, we used the “See all similar articles” function in PubMed for these 5 previously identified articles; this yielded 1 new article meeting our inclusion criteria. We also reviewed bibliographies of each identified article, which yielded 1 additional new article, for a total of 7. We reviewed the full text of each identified article and extracted information including author, year of publication, sample size, exposure definition, scanner type, MRI outcomes, covariates, and key findings.

Results

We identified 7 studies that met our inclusion criteria, all of which were observational in design and published between 2013 and 2021. Table 1 presents extracted information. Included preterm infants were born at or below 33 weeks’ gestation. Sample sizes ranged from 22 to 377 infants. Exposure to human milk included both maternal and donor milk and was defined in various ways including continuous and categorial variables. No study included a full-term comparison group. There were three main MRI outcome domains: 1) white matter integrity, assessed with diffusion tensor imaging (DTI), resting state functional connectivity, or semi-automated segmentation of white matter abnormality; 2) total and regional brain volumes; and 3) cerebral vascularity.

Studies revealed associations of greater exposure to human milk vs. formula with more favorable white matter-based outcomes. For example, Pogribna et. al. reported that a longer duration of human milk use was associated with greater fractional anisotropy (FA), a measure of white matter integrity, in the corpus collosum (3.7 weeks more advanced FA per 10 additional days human milk feeding, 95% CI, 1.9, 5.6 with adjustment for comorbidities and other confounders).[24] Similarly, Blesa et. al. reported that receiving exclusive human milk on ≥75% or ≥90% of days, compared with <75% or <90%, was associated with higher FA in several early-myelinating white matter tracts,[25] as well as greater connectivity within and between brain regions. Also with respect to connectivity, Niu et al used resting state functional connectivity and found that the temporal lobe, particularly the right temporal lobe, had greater global connectivity efficiency in breastfed infants.[26] Regarding signal abnormality within the periventricular and subcortical white matter, regions that are particularly vulnerable among preterm-born infants, Parikh et. al. found that receiving maternal milk at discharge was associated with less extensive diffuse abnormality, even after adjusting for co-morbidities and other potential confounders.[27]

Regarding regional brain volumes, studies reported that greater exposure to human milk was associated with larger volumes of the deep nuclear gray matter,[6] hippocampus and amygdala,[6,28] and cerebellum.[28]

In the sole study examining cerebral vasculature,[29] greater human milk was associated with more advanced cerebral arterial vessel tortuosity.

Discussion

This narrative review reveals the emerging use, over the past decade, of MRI as a tool to investigate the influence of human milk during a vulnerable period of rapid brain development in the very preterm infant. This literature focused on structural brain development complements a body of epidemiologic evidence linking human milk feeding in the NICU with neurodevelopmental outcomes [4–6] and re-affirms the conclusion that this practice is beneficial.[7]

The studies identified in this review can be viewed within the broader neurobiological context of cerebral white matter injury, neuronal dysmaturation, and their MRI correlates in preterm-born infants. Typical brain MRI findings in preterm-born infants, as compared with full term infants, include punctate lesions in the white matter, altered microstructure (delayed FA increase in cerebral white matter, delayed FA decrease in cerebral cortex), reduced volumes of several brain regions, impaired connectivity, and decreased cortical surface area and folding.[30] These abnormalities result from the effects of an initial insult, such as hypoxia-ischemia or inflammation, followed by secondary dysmaturation. Primary dysmaturation in the absence of white matter injury also occurs.[31] Taken together, studies identified in this review demonstrate that human milk feeding is associated both with less injury (e.g. less volume of diffuse white matter abnormality evident at term equivalent age)[27] and with less dysmaturation across multiple brain regions and processes including the early stages of myelination, connectivity, and tissue expansion in the deep nuclear gray matter, hippocampus, amygdala, and cerebellum. Although one study reported more advanced cerebral artery vessel tortuosity, more data are needed before firm conclusions can be made about this aspect of preterm brain development. Overall, rather than a signature pattern specific to human milk, MRI evidence suggests a reduction in typical preterm birth-associated structural brain abnormalities.

All studies identified in this review were observational in design, which is justified since it is not feasible to randomly assign an infant to receive their own mother’s milk vs. formula. The main limitation of this approach is confounding by shared determinants of human milk feeding and brain injury and dysmaturation. Some[6,24,27,28] but not all studies attempted to measure and adjust for medical confounders such as gestational age whereas adjustment for social factors was limited to just 2 studies.[6,24] An important social factor to consider is parent engagement in care of the infant. High levels of parent engagement across multiple domains of infant care promote both greater breastfeeding and greater infant weight gain,[32] which is linked with improved structural brain development[33,34] but no study identified in this review measured or adjusted for any aspect of parent presence or engagement. Overall, the existing literature regarding maternal milk remains limited by a lack of rigorous measurement of and adjustment for key confounders, including both medical and social factors

In contrast to studies of maternal milk vs. formula, it is feasible to randomly assign infants to supplementation with donor milk vs. formula when maternal milk is in short supply or unavailable.[35] We did not identify any randomized supplementation trials that used brain MRI at term equivalent age as an endpoint, although one observational study[28] identified in our review noted that some apparent benefits of maternal milk also extended to donor milk. In the specific case of donor milk, future opportunities exist to apply brain MRI in randomized trials that minimize confounding by design.

This review highlights the current application of brain MRI to shed light on the effects of human milk overall. Additionally, specific components of human milk may have neuroprotective or neurorestorative potential in the very preterm infant. Pre-clinical models indicate that milk fat globule membrane, lactoferrin, HMOs, microbes, osteopontin, and milk exosomes all hold promise in this regard.[11–18] Translation of this science to human infant populations is underway, with early evidence of neurodevelopmental benefits resulting from adding myriad milk bioactives to term formula.[36–39] However, those findings cannot be generalized to very preterm-born infants given differences in developmental timing, susceptibility to brain injury, and underlying nutritional vulnerabilities. For donor milk, which is used mainly for very preterm infants, alteration of nutrients and bioactives during pasteurization[40] may attenuate its benefits as compared with unprocessed maternal milk. Brain MRI has proven useful in defining the effects of individual milk bioactives on structural brain development in animal models, including the pig;[15,41] those studies point to imaging biomarkers that may also be useful in human infants, including those born very preterm.

Moving forward, both carefully designed observational studies and well-controlled interventional studies can shed light on the role of specific milk bioactives and combinations thereof, fed during the preterm period. Applying quantitative brain MRI has the potential to speed the process of identifying promising interventions, which could then be prioritized for study in large clinical trials powered for longer-term neurodevelopmental outcomes. Brain MRI findings at term equivalent age could specifically inform study design with respect to the selection of neurodevelopmental outcomes. Additionally, consistency between findings on MRI at term equivalent age and neurodevelopmental outcomes, particularly in studies that are well-controlled for confounders, adds to the overall strength of evidence in favor of neuroprotective or neurorestorative properties of human milk and/or specific components thereof.

Conclusions

In this narrative review, we present evidence suggesting that human milk may protect the preterm brain from the white matter injury and dysmaturation to which this infant population is vulnerable. Brain MRI at term equivalent age is emerging as a useful tool to investigate the effects of human milk on brain development in preterm infants. This approach, when grounded in neurobiological knowledge about preterm brain injury and development, may allow further insight into the mechanisms and pathways underlying beneficial associations of human milk with neurodevelopmental outcomes in this population. Brain MRI also

holds promise within clinical investigations of specific milk bioactive components with neuroprotective or neurorestorative potential.

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Table.

Original research using MRI to investigate brain development in relation to human milk exposure during the preterm period.

First author	Year	Gestational age	N*	Exposure definition	Scanner type	MRI outcomes	Covariates	Summary of key findings
1) Pogribna	2013	≤29 weeks	86	Duration of human milk use, days	Philips Achieva (3T)	DTI Regions of interest: - anterior & posterior limbs of internal capsule - frontal & occipital periventricular zones - centrum semiovale - genu - splenium of corpus callosum - subventricular zone Control regions of interest: - external capsule -middle cerebellar peduncles	- Maternal hypertension - Private insurance - Outborn status - Antenatal steroids - Chorioamnionitis - Rupture of membranes duration - Hypothermia - Birth weight - Caucasian - Sex - White matter injury on ultrasound - NEC - PDA - Duration of caffeine therapy - Duration of mechanical ventilation	- Longer duration of human milk intake associated with greater FA maturation of corpus collosum (3.7 weeks per 10 days, 95% CI 1.9, 5.6)
2) Vasu	2014	<32 weeks	22	1) mL/kg/day, early (first week of life) and total (birth to 34+6 weeks PMA) 2) percent enteral diet as human milk	Philips Achieva (3T)	1) Total brain volume 2) Proximal cerebral arterial vessel tortuosity (CAVT) score	- Age at scan	- Early human milk intake positively correlated with CAVT score (r=0.31, p=0.18) - Total human milk intake positively correlated with CAVT score (r=0.44, p=0.05) - Percent enteral diet as human milk positively correlated with CAVT score (r=0.45, p=0.04)
3) Belfort	2016	<30 weeks	147	In first 28 days: 1) number of days with enteral intake >50% maternal milk 2) mean mL/kg/day maternal milk	General Electric Signa Echospeed (1.5T)	Brain volumes - total - gray matter - white matter (myelinated, unmyelinated) - deep nuclear gray matter - cerebellum - hippocampus	- Sex - Age at scan - Gestational age - Social risk - Neonatal illness	- Positive association of days enteral intake >50% maternal milk with deep nuclear gray matter volume (0.15 cc per day, 95% CI 0.05, 0.25) - Positive association of mean maternal milk intake with hippocampus volume (0.02 cc per 10 mL/kg/day, 95% CI 0.004, 0.03)
4) Blesa	2019	≤33 weeks	47	Percent of days receiving exclusive	Siemens MAGNETOM Verio (3T)	1) Edgewise connectome 2) Network analysis	None	- Increased FA-weighted connectivity in ≥75% and ≥90%

First author	Year	Gestational age	N*	Exposure definition	Scanner type	MRI outcomes	Covariates	Summary of key findings
				breast milk ≥75% or ≥90% vs. <75%		3) Tract based spatial statistics 4) Brain volumes - total - brainstem - cerebellum - cortical gray matter - deep gray matter - white matter		vs. <75% (connections involved intra- and inter-hemispheric frontoparietal and limbic system structures); also subcortical networks in ≥90% vs. <75% - Higher FA in major white matter tracts (splenium, centrum semiovale, corticospinal tracts, arcuate fasiculi, posterior limbs of internal capsule) in ≥75% and ≥90% vs. <75%
5) Ottolini	2020	≤32 weeks	68	Primarily breast milk or formula (>50% total enteral intake) Secondary analysis of donor milk vs. formula	General Electric Discovery (3T)	1) Brain volumes - total - cortical gray matter - white matter - deep gray matter - amygdala-hippocampus - cerebellum - brainstem 2) Diffusion tensor imaging	- gestational age - age at scan - average weight gain	- Larger volumes of total brain, amygdala-hippocampus, cerebellum in human milk vs. formula - Larger amygdala-hippocampus in donor milk vs. formula - lower MD in corpus callosum, R & L PLIC, middle cerebellar peduncle; lower FA in cerebellar vermis in human milk vs. formula - lower MD in corpus callosum, L PLIC, middle cerebellar peduncle, lower FA in cerebellar vermis in donor milk vs. formula
6) Niu	2020	≤33 weeks	50	Breastmilk >75% vs. <75%	Siemens Avanto (1.5T)	Resting state functional connectivity	None	Breastmilk positively correlated with - temporal global efficiency (r=0.362, p=0.014) - temporal nodal efficiency of bilateral caudate (r=0.439, p=0.002), right middle temporal gyrus (r=0.421, p=0.004), right inferior temporal gyrus (r=0.319, p=0.031), right insula gyrus (r=0.355, p=0.016), left thalamus (r=0.539, p=0.0001)

First author	Year	Gestational age	N*	Exposure definition	Scanner type	MRI outcomes	Covariates	Summary of key findings
7) Parikh	2021	≤32 weeks	377	Exclusive maternal milk at discharge	Philips Ingenia (3T)	Volume of diffuse white matter abnormality (DWMA)	- Pneumothorax - Severe bpd - Severe rop - Dexamethasone - Caffeine - White matter abnormality score - Sex - Age - Center	Exclusive maternal milk associated with lower DWMA score

*Sample size with neuroimaging data, may be lower than total cohort sample size

DTI is diffusion tensor imaging, FA is fractional anisotropy, MD is mean diffusivity, NEC is necrotizing enterocolitis, PDA is patent ductus arteriosus