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Review

Neurodevelopmental outcomes and nutritional strategies in very low birth weight infants

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SUMMARY

The developing brain of the very low birth weight (VLBW) infant is highly sensitive to effects of the nutritional milieu during the neonatal hospitalization and after discharge. Strategies to optimize nutritional care play an important role in reducing long-term neurodevelopmental morbidities in this population. Currently available interventions to ensure that the unique nutrient requirements of the VLBW infant are met include various dietary fortification strategies and parenteral nutrition. In this article, we review evidence regarding nutritional strategies and their beneficial effects on neurodevelopment in VLBW infants. We also highlight gaps in current knowledge and areas of current investigation that hold promise for improving nutritional care and long-term outcomes.

1. Introduction

Although growth of hospitalized preterm infants has improved substantially in the past two decades, poor weight gain remains the most frequent morbidity seen in very low birth weight (VLBW, <1500 g) infants. For example, epidemiologic data from across the USA demonstrate that in 2013, over half of VLBW infants left the neonatal intensive care unit (NICU) with a weight below the 10th percentile for gestational age [1]. Another recent study from 132 California NICUs reported that VLBW infants lose on average almost a full standard deviation in weight-for-age from birth to discharge [2], demonstrating extrauterine growth that lags behind the growth that would have occurred in utero. Taken together, these findings suggest that despite the current emphasis on intense early nutritional support, undernutrition remains an important problem for hospitalized VLBW infants.

Another frequently occurring morbidity seen in VLBW infants is neurodevelopmental impairment. VLBW infants demonstrate difficulties across a wide range of domains, including cognitive, motor, language, and behavioral functioning [3,4]. These difficulties burden children and their families, and incur large societal costs related to early intervention and special education services [5]. Notably, links between neurodevelopment impairment and early nutrition are well established [6], and are explained by the sensitivity of the developing brain to nutrition [7].

For the VLBW infant, developmental processes that normally take place in utero instead occur after birth, in the NICU environment. Magnetic resonance imaging (MRI) studies provide a window into the rapid growth and development of the preterm brain that occur during this time. From 29 weeks of postmenstrual age (PMA) to term equivalent, the preterm brain increases in volume from 150 to 400 mL, reflecting a rapid expansion of both the white and gray matter [8]. Structurally, the brain surface transforms from being largely smooth at 25 weeks of gestation to demonstrating a nearly-mature pattern of sulci and gyri by term equivalent age (Fig. 1) [9,10]. On a microstructural and cellular level, the predominant developmental processes immediately after very preterm birth include dendritic and axonal growth and differentiation of the myelin-producing oligodendrocytes. Close to term equivalent age and into the first year of life, synaptic pruning and myelination become prominent [11].

Certain developmental processes may be more or less vulnerable to undernutrition, thus the timing of the limitation in nutritional support is an important determinant of its long-term impact. Also, although the potential for recovery after a period of undernutrition exists, certain aspects of brain development may be permanently altered by a limited nutritional exposure during a critical period. Clinicians who care for very preterm infants must therefore understand the key role that nutritional care plays in optimizing the neurodevelopmental outcomes of their patients.

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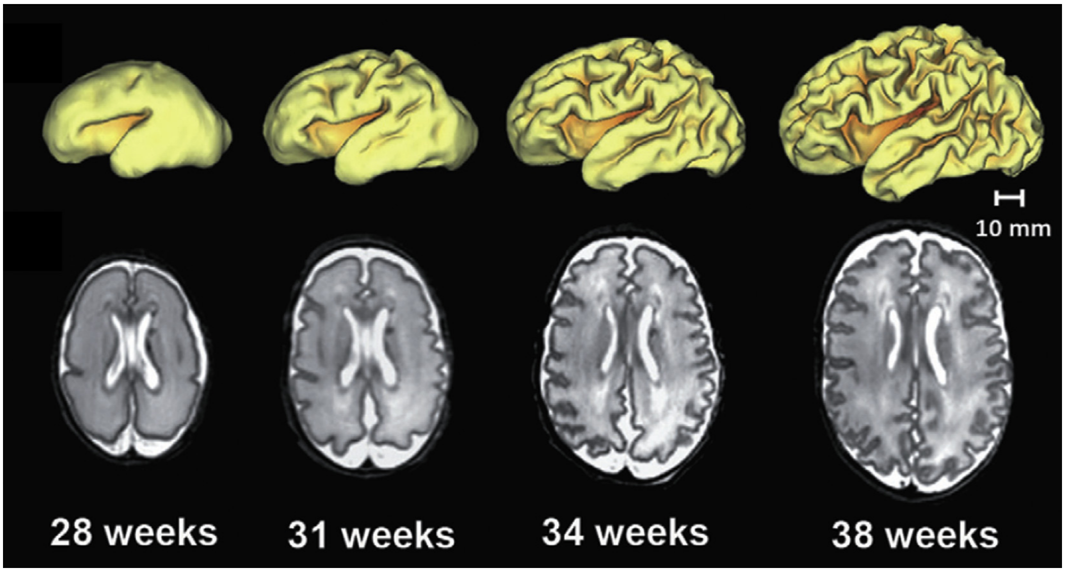

Fig. 1. Growth and development of the preterm brain. These images were obtained from a single infant at 28, 31, 34, and 38 weeks of postmenstrual age, and demonstrate the marked increase in brain size and complexity of cortical folding over this time period. From Smyser et al. [10].

During the neonatal hospitalization, although the optimal rate of growth is unknown, the goal is to match the rate of growth and body composition of the in-utero fetus [12]. Available interventions include enteral and parenteral feeding strategies, as well as micronutrient and fatty acid supplementation. The first year after hospital discharge provides an opportunity to address nutrient and growth deficits that may have accrued during the hospitalization, with the potential to ameliorate adverse long-term effects. Interventions include specialized formulas and fortification of human milk. In this article, we review the evidence base behind nutritional strategies during and after the neonatal hospitalization, with a focus on interventions that show promise to improve neurodevelopmental outcomes (Table 1). We point out both key practice points and areas requiring additional research.

2. Nutritional strategies during the NICU hospitalization

Clinicians in the NICU play a critical role in ensuring that VLBW infants receive nutritional care that is targeted to their unique needs. In reviewing the evidence base behind nutritional practices in neonatal intensive care, it is notable that many nutritional intervention studies have focused on short-term growth outcomes, whereas relatively few have determined longer-term effects of nutritional interventions on neurodevelopment. To fill this gap, longitudinal observational studies provide information that complements data from randomized trials. Clinicians should recognize that knowledge alone is not sufficient to ensure the effectiveness of nutritional interventions; implementation requires processes of care that support consistent care and attention to nutritional priorities [13]. In this section, we review enteral and parenteral nutrition strategies with a specific focus on the evidence base that established their effects on somatic growth and neurodevelopment (Table 1).

2.1. Fortified preterm formula

Seminal research by Lucas and colleagues conducted in the 1980s established that providing a formula enriched with

Table 1
Evidence for effects of nutritional strategies on growth and neurodevelopmental outcomes in very low birth weight infants.

	Weight gain and/or linear growth	Head growth	Neurodevelopmental outcomes
During the NICU hospitalization			
Fortified preterm vs term formula	+	+	+
Modifications to preterm formula			
Higher protein	+	↔	?
Long chain polyunsaturated fatty acids	↔	↔	+/↔
Bile salt-stimulated lipase	↔	↔	?
Human milk vs formula	−	−	+
Human milk fortification vs no fortification	+	+	+
Adjuncts to human milk fortifier			
Added protein	+	+	?
Human milk cream	+	+	?
Maternal DHA supplementation during lactation	↔	↔	+
Parenteral nutrition (early vs late)	+	↔	↔
Iron supplementation	↔	↔	↔
After NICU discharge			
Transitional (post-discharge) vs term formula	+	↔	↔
In-hospital preterm vs term formula	+	+	↔
Human milk fortification	+	+	+/?

+, positive association; −, negative association; ↔, no association; ?, little or no evidence; NICU, neonatal intensive care unit; DHA, docosahexaenoic acid.

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