Protein Intake and Neurodevelopmental Outcomes

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KEYWORDS

• Protein • Neonatal • Prematurity • Outcomes • Neurodevelopment

KEY POINTS

- Biologic factors associated with prematurity impede the ability to achieve current recommended protein intake for preterm infants in the first week of life.
- Recognition of potential deleterious effects of nutritional deprivation among extremely preterm infants has resulted in recommendations for increased parenteral amino acid intake.
- There is evidence of benefit of early protein intake on head circumference growth among preterm infants.
- Further studies are needed to clarify the relationships among early protein intake, early head growth and neurodevelopmental outcomes, and the differential effects of gender.

There is a continuously accumulating body of evidence that suggests that malnutrition during critical periods of brain growth and development alters the growth trajectory of the developing brain and can have permanent negative developmental consequences.[1–3] Although a great deal of indirect evidence points to the importance of protein intake for the developing brain, there still exists very little direct evidence of the effects of protein intake on neurodevelopment.

In humans, the most critical developmental period of brain growth and function occurs during the third trimester of pregnancy and the first 2 years of postnatal life.[1,4] During this period, brain growth and development are occurring more rapidly than at any other time in life. At 20 weeks' gestation, the brain weighs only 10% of what it weighs at term and is completely smooth, with only the Sylvian fissure having

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formed. The brain increases in weight in a linear fashion from 20 to 40 weeks, and in the process, develops all remaining gyri and sulci.[5] The volume of the cortical gray matter increases 4-fold from 29 to 40 weeks' gestation, and a 5-fold increase in white matter volume occurs from 35 to 40 weeks.[6] In addition to neuron formation, migration, maturation, synapse formation, and pruning via apoptosis are all occurring rapidly during this period and continue to occur throughout and beyond the neonatal period. The rapid changes associated with these developmental processes make the developing brain extremely vulnerable to environmental perturbations.[1,4]

One such environmental perturbation with the potential to have lasting effects on the developing brain is an alteration in nutritional intake. In studies of malnutrition in rat pups, even mild malnutrition during this "critical period" in brain development, resulting from a larger than normal litter size, led to deficits in neuron formation in the cerebellar granular layer and deeper layers of the cerebral cortex.[1] In preterm human infants with birth weights less than 1750 g, caloric deprivation (defined as intakes of <85 kcal/kg/d) has been directly related to poor head growth, and prolonged periods of caloric deprivation (greater than 4 weeks in duration) has been associated with lower scores on the Bayley Psychomotor Developmental Index (PDI) at 12 months of age.[7]

Thus, the provision of adequate nutrition to infants during the neonatal period seems to be critical. Despite this, nutritional practices vary greatly among neonatal intensive care units (NICUs), and energy-containing macronutrients (protein, carbohydrate, and lipid) have historically been introduced slowly and increased cautiously because of concerns for intolerance. This intolerance results in a period of nutritional deficiency that is common and accepted as inevitable for newborns hospitalized in the NICU.[8,9] Although all hospitalized newborns are vulnerable, those born preterm are the most vulnerable and the most studied in the published literature.

The precise nutritional needs of the preterm infant are still unknown, as are the duration and degree of undernutrition that places the infant at neurodevelopmental risk. The American Academy of Pediatrics Committee on Nutrition recognizes the importance of adequate nutrition for these vulnerable infants and recommends providing sufficient energy and nutrients to meet the requirements of the growing fetus with the goal of "approximating the rate of growth and composition of weight gain for a normal fetus at the same postmenstrual age."[10,11] Nevertheless, there are several challenges encountered when attempting to achieve nutrient intake in preterm infants commensurate with the intrauterine environment. Gastrointestinal constraints result in delays in achieving full enteral feeds. Small stomach capacity, slow gastric emptying, decreased intestinal motility, decreased enzyme production, immature sucking, and diminished suck-swallow coordination contribute to potential nutritional deficits associated with enteral feeds. Ehrenkranz and colleagues[12] showed that age of first enteral feed was inversely related to birth weight. Parenteral alimentation, therefore, is the initial primary method for providing early nutrition, including protein to very preterm infants, and even with the provision of parenteral nutrition, there remains a difference between the nutrient supply that the normally growing fetus typically receives and that received by the postnatal, preterm counterpart.

The composition of the nutrients delivered by the placenta reflects the unique needs of the growing fetus. Glucose is delivered at a rate that reflects energy use; amino acid uptake is high and far exceeds that needed for accretion (oxidation of the excess is used as a significant energy source), and lipid uptake is minimal. The typical neonate in the intensive care unit receives high rates of glucose and lipid infusion in an attempt to provide adequate calories for growth, yet lower of rates amino acid/protein infusion.[13,14] This practice of limiting protein intake is especially commonplace in the