Prevention of protein deprivation in the extremely low birth weight infant: a nutritional emergency

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Insufficient nutrient supply in preterm infants and protein deprivation in particular can represent a nutritional emergency. It can cause many of the features of the starvation response, including insulin resistance and hyperglycemia, as well as growth failure and neurological injury. At Baylor University Medical Center, we began providing intravenous protein on the first day of life to extremely low birth weight infants in 2000. This has led to significant improvements in the time to regain birth weight and the rate of daily weight gain during the first month of life. While neonatologists traditionally focus first on newborns' warmth, respiratory support, and cardiovascular support, early aggressive nutrition support, in the form of intravenous amino acids at time of admission as well as glucose, is of great benefit and should be a standard element in the initial care of the extremely low birth weight infant.

Extremely low birth weight (ELBW) infants who weigh <1000 grams at birth represent only 19% of total admissions to the neonatal intensive care unit (NICU) at Baylor University Medical Center (BUMC) yet contribute more than 40% of the patient days. These smallest of newborns not only have prolonged hospital stays but also suffer both short- and long-term morbidities that can affect them for the rest of their lives. For example, at birth, only 18% of ELBW infants fall below the 10th percentile in growth, yet by the time of discharge almost 90% fall below the 10th percentile. This is called iatrogenic postnatal growth deficiency. These somatic changes often persist after discharge, with 40% of infants at 18-month follow-up remaining below the 10th percentile (1). In addition, these infants are subject to long-term neurological injury (2). Clear evidence from animal studies and increasing long-term clinical evidence from neonatal studies indicate that early malnutrition and especially protein deprivation in the early hours after birth may be one of the key factors contributing to poor long-term neurological outcomes (3, 4).

It has been shown since the 1960s that the infusion of intravenous glucose improves survival of preterm infants. The late second trimester and early third trimester fetus born prematurely, between 22 and 28 weeks, is suddenly cut off from a rich nutrient supply by way of placental flux, primarily of glucose and amino acids. Experimental evidence shows that 4 g/kg/day of transplacental amino acids are transferred to the fetus at this point in gestation when fetal growth is at its most rapid (5). Up to 50% of the protein is used for energy and the remainder for tissue growth. The sudden cessation of this critical supply at the time of birth results in endogenous protein loss, or proteolysis, in an effort to meet basal metabolic needs of the ELBW infant.

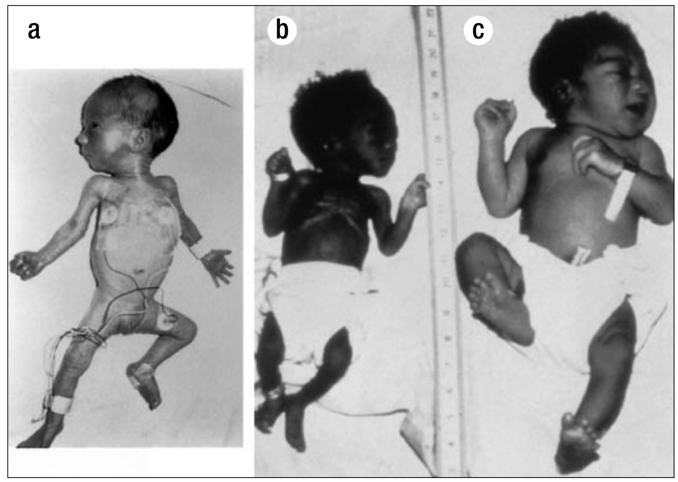

Figure 1. (a) A preterm infant compared with **(b)** a full-term growth-restricted infant and **(c)** a full-term normally grown infant. Both the preterm and the growth-restricted infant have little in the way of fat or glycogen stores and will not tolerate nutrient deprivation. Reprinted with permission from reference 7.

Little fat or glycogen is stored at this point in gestation. Thus, the only way that the ELBW infant can maintain sufficient glucose supply to meet its metabolic needs (most importantly for the brain) is either from exogenous glucose in the form of intravenous dextrose solutions or from endogenous protein catabolism. The metabolic pathways that are triggered when there is insufficient nutrient supply result in many of the features of the starvation response, including insulin resistance

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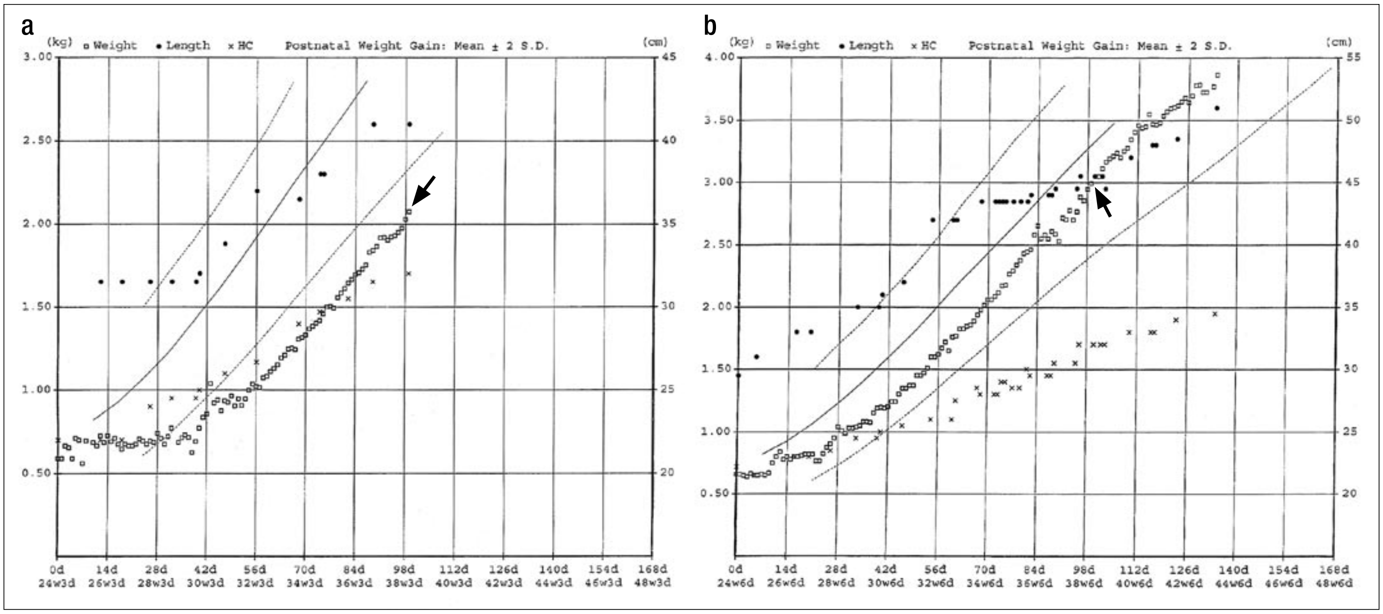

Figure 2. Typical growth patterns of extremely low birth weight infants in the Baylor University Medical Center neonatal intensive care unit: **(a)** preintervention, in 1999, and **(b)** postintervention, in 2003. Note the different vertical scales. Growth in (a) falls below the 10th percentile and does not recover, whereas growth in (b) remains above the 10th percentile. The infant in (a) weighed just over 2 kg on day 98 (arrow), whereas the infant in (b) weighed 3 kg on day 98 (arrow). The gestational age and birth weight of both infants were similar.

and hyperglycemia (6). The latter problem is common in the ELBW infant and seems to be attenuated when sufficient intravenous protein is supplied.

It is estimated that a 1-kg infant has total body stores of only 88 g of protein, mainly in the form of skeletal muscle *(Figure 1)*. Without exogenous protein, 1% to 2% per day of this is lost due to proteolysis. The steady loss of this much protein can result in large protein deficits that are extremely difficult to replenish. For example, a 1-kg infant with no protein intake and a glucose infusion of 10% dextrose at 100 mL/kg/day will receive only 34 Kcal/kg/day (less than basal metabolic needs of 50 to 60 Kcal/kg/day) and each day develop a protein deficit of 1 to 1.5 g of protein. After 4 days of absent protein intake, a deficit of 4 to 6 g develops. During this same time, the fetus would have had a 2 g/day net increase in protein. Simply stated, the infant with no exogenous source of protein will have a net deficit of 12 to 14 g of protein within a few days of birth unless exogenous protein is provided. This represents a >15% protein loss in a 1-kg infant. These amounts are very difficult to make up. Further, these deficits are occurring at a very critical point in organ growth.

Increasing evidence suggests that not only do these protein deficits affect somatic growth adversely for life but, more distressingly, the brain itself suffers irreversible changes at a critical time in development (8). Very interesting evidence also suggests that epigenetic changes in cellular DNA may result from protein malnutrition during vulnerable and critical periods of growth and seem to have adverse effects in the adult—e.g., the intrauterine growth-retarded infant (Figure 1b) correlates with adult metabolic syndrome (9). Further, these effects on the genome may be transgenerational (9).

Recent clinical studies have demonstrated the safety and feasibility of providing immediate intravenous protein to ELBW infants who are critically ill in the NICU (10–13). There have been concerns that the infant would not tolerate intravenous protein in the form of crystalline amino acids and would develop metabolic acidosis, hyperammonemia, azotemia, and abnormal and potentially neurotoxic levels of amino acids. In the past, protein hydrolysates of fibrin or casein were associated with these detrimental outcomes, but the newer preparations seem free of these side effects. These newer amino acid solutions, specially formulated for the newborn, have proven safe and effective, permit positive nitrogen balance, and are able to prevent the devastating protein catabolic losses described above.

The Nutrition Committee of the American Academy of Pediatrics has stated that the goal of neonatal nutrition should be the maintenance of the intrauterine growth rate (14). This goal guides modern neonatal nutritional care.

EXPERIENCE AT BAYLOR UNIVERSITY MEDICAL CENTER

An aggressive early parenteral nutrition program was introduced to the NICU at BUMC in 2001. The goal was to mitigate the protein deficit resulting from delayed protein administration in the critically ill newborn. The measures used to determine the effect of this program were time to regain birth weight and the rate of weight gain over the first 30 days of life.

One percent crystalline amino acid in 10% dextrose solution was stocked and available as the admission fluid for all infants, including ELBW infants. We compared growth in 27 consecutively admitted ELBW infants from 1999, before the program was initiated, and 2003, after the program was introduced.

A typical growth curve from 1999 is compared with a typical growth curve from 2003 *(Figure 2)*. In 1999, the daily weight gain was 7 g/kg/day; in 2003, it was 12 g/kg/day. Similarly, in 1999, birth weight was regained in 12 days, but by 2003, after the availability of admission total parental nutrition, the time

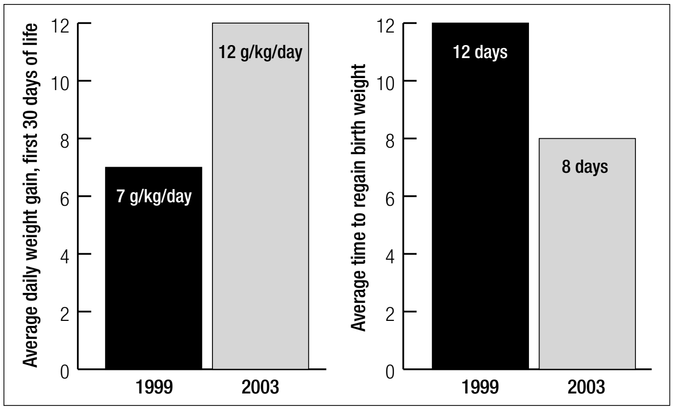

Figure 3. Weight changes before (1999) and after (2003) the addition of intravenous protein to the nutritional support of extremely low birth weight infants at Baylor University Medical Center.

was reduced to 8 days *(Figure 3)*. These changes are statistically significant at $P \leq 0.05$ using the Student t test.

CONCLUSION

Our experience has shown that provision of early intravenous amino acids to the ELBW infant on admission to the NICU will result in improved short- and long-term somatic growth. These findings are consistent with the observations of others (3, 4).

Failure to provide adequate amino acids to the ELBW infant will result in a metabolic and nutritional emergency. The resulting devastating proteolysis and negative nitrogen balance to which these vulnerable infants are so prone can now be prevented. Intravenous amino acids upon admission to the NICU are considered to be essential. This is most optimally accomplished with stock solutions of amino acids in dextrose. Recent evidence suggests that more concentrated amino acid solutions would be even more effective, and BUMC now plans to provide 3 g/kg/day amino acid to ELBW infants on admission.

The medical decisions made in the first hours of life have traditionally centered on provision of warmth, respiratory support, and cardiovascular support. Nutritional needs of the newborn have generally been secondary. Typically, several days of "stabilization" elapsed before adequate nutrition was provided, and then protein was increased in a stepwise fashion by 0.5 g/kg per day. With the increasing acceptance of the importance of adequate protein intake during vulnerable and critical periods in human development, early aggressive provision of protein to the ELBW infant must take its rightful place alongside these other "tried and true" areas of neonatal intensive care in order to obtain the best possible outcome for our tiniest of patients. The beneficial effects will last a lifetime.

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