Case Presentation for the Course in Clinical Nutrition

GESKES/ SSNC

Individualized Nutritional Support in the Case of Postnatal Growth Restriction

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1. Summary

Optimizing postnatal growth is a primary concern of the neonatologist and pediatrician.

Despite advances in nutritional support postnatal growth of the very low birth weight infant (less than 1500 g at birth) remains suboptimal in many cases. I present the case of a growth restricted preterm infant, who was put on an individualized enteral diet to enable better postnatal growth. The effects of the diet were assessed biochemically with amino acid profiles.

2. Key Words

Intrauterine growth restriction, very-low-birth-weight infant, extrauterine or postnatal growth restriction, individualized diet

3. Abbreviations

BM: brest milk; VLBW very low birth weight; WHO world health organisation

4. Introduction

Suboptimal postnatal growth as well as intrauterine growth restriction is associated with the development of arterial hypertension, coronary artery disease, diabetes type 2, metabolic syndrome and adiposity in adulthood (1). In animal models as well as in preterm infants inadequate nutrition in the early postnatal phase also has been shown to lead to impaired neuro-cognitive development (2). Thus, one of the neonatologist's main concerns is optimizing the infant's postnatal growth.

Frequently the freshly born preterm infant is unstable during the first days of life, due to various acute diseases (such as respiratory distress syndrome, sepsis or generalized inflammatory syndromes) leading to delays in establishing and maintaining adequate enteral nutrient intake. This in turn results in nutrient deficits, especially in protein, but also in calcium-phosphate deficiency. The clinical course is then often marked by postnatal growth restriction and several associated morbidities.

Currently the intrauterine growth curves are considered as goals for postnatal growth during the early infant period. With the available parenteral nutrition and expressed breast milk of the infant's mother, these growth curves cannot easily be attained. (2, 3). Hence it is recommended to fortify expressed breast milk (4).

Various medical societies and committees advocate feeding expressed breast milk as opposed to formula milk since there is growing evidence of distinct health benefits to feeding human milk, such as less mortality, less septic episodes, fewer occurrences of infections and better neurological outcome (2, 3, 4, 5,6).

For these reasons we start enteral feeds with expressed breast milk within the first hours of life with a partial parenteral nutrition in parallel.

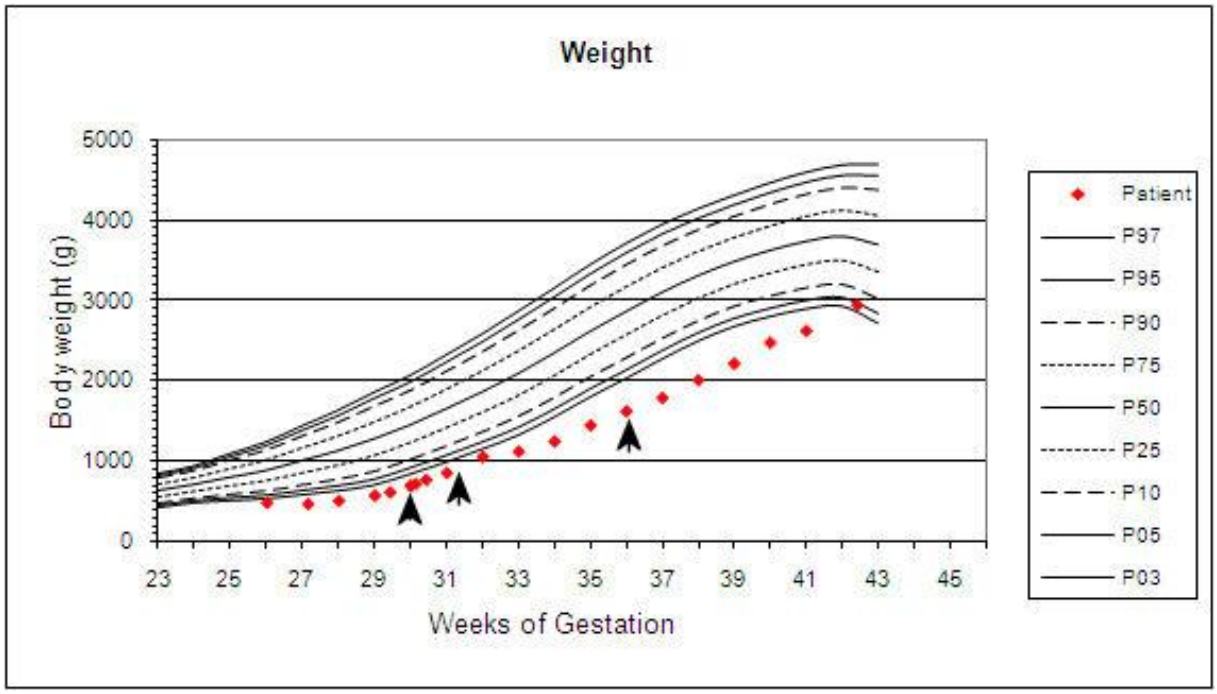
5. Case Presentation

S.L was born at 26 0/7 weeks gestational age with a birth weight of 480 g with 2.7 SD below the 3rd percentile. This boy was born to a healthy second gravid 1st parity mother of 21 years. The pregnancy was marked by an early detection of growth restriction. The amniocenteses at 22 3/7 weeks revealed a normal XY karyotype. As of the 24th gestational week the mother noted recurrent vaginal bleeds. A retrochorial hematoma could be documented with ultrasound and possibly a singular umbilical artery. Because of continued intrauterine growth restriction and recurrent vaginal bleeds the mother was hospitalized for prophylactic steroid treatment at 24 4/7 weeks. At 25 6/7 weeks she developed uterine contractions besides the known light vaginal bleeds. In light of the severe growth restriction and intensifying vaginal bleeds the baby was delivered by primary cesarean section. He adapted well with APGAR values of 7/9/9 at 1, 5 and 10 minutes respectively. He was admitted to our neonatal intensive care ward under continuous positive airway pressure support. The intrauterine growth restriction most likely resulted from chronic retrochorial bleed, which in turn led to placental insufficiency. This was confirmed on placental histology. Clinically there were no signs of a syndrome.

The infant received a peripheral intravenous vascular access and was started on standard care with 12,5 % Glucose and 0.5 g Protein per kilogram body weight as well as tailored electrolytes during the first minutes of life. Within a few hours of delivery he was also started on donated expressed breast milk at 20 ml /kg body weight. He tolerated increasing enteral feeds until a total amount of 160 ml /kg /day, whilst all the parenteral amounts were being decreased. The milk was switched to his own mother's milk once her milk production was sufficient. As of the 3rd day of life he presented recurrent hyperglycemic episodes. This was treated conservatively by reducing the intravenous glucose amount from 8 mg/kg body weight/ min to 5 mg /kg/min. Once the parenteral nutrition was ended on day of life 16, we proceeded to enrich the expressed maternal breast milk with a human milk fortifier FMS® (Milupa breast milk supplement), which is a standard procedure. Once again the infant presented hyperglycemic episodes with values reaching 11.1 mmol/L.

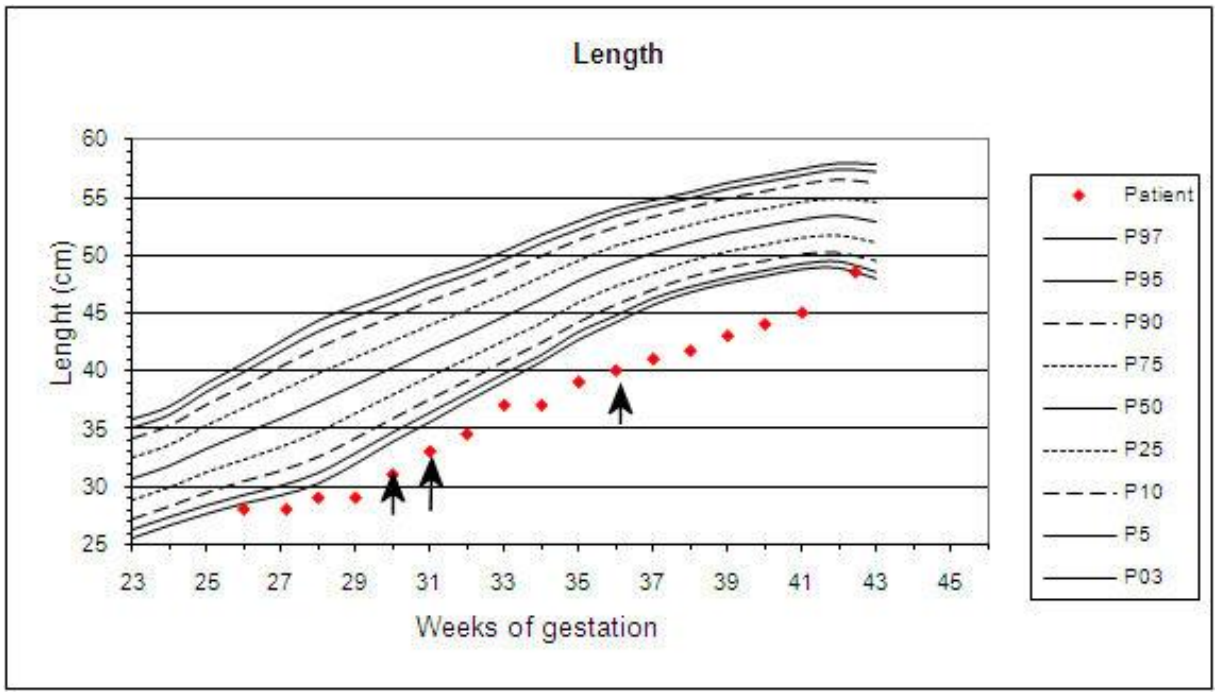
We were faced with an extremely growth retarded infant, who was showing an unsatisfactory postnatal growth pattern. (See growth chart in figures 1 and 2 during the first four weeks of life).

Fig 1



Percentile figure with weight in grams. Arrowheads indicate start of special diet, adjusting of special diet and end of special diet.

Fig.2



Percentile figure with body length in cm. Arrowheads indicate start of special diet, adjusting of special diet and end of special diet.

At 4 weeks of age the protein intake, calculated at 1.6 g/kg/day, was deemed insufficient in light of a markedly reduced urea and the above mentioned limited growth.

Because of the development of a mild chronic lung disease, where he required supplemental oxygen (initially via continuous positive airway pressure for a total of 47 days and maximally 0.3 FiO2, then as of 32 5/7 weeks corrected age via nasal cannula up until 40 6/7 weeks corrected age), we were loath to increase the feeding volumes beyond 160-170 ml/kg to avoid volume over load.

In order to achieve better caloric intake without increasing carbohydrates to intolerance levels and optimize protein intake, we proceeded to enrich the mother's milk with half the usual amount of FMS® (Milupa breast milk supplement at 2.1 %, instead of 4.2%) as well as UCD® (protein powder for urea cycle defect) to approximately 2.3g Protein/ kg/ day plus Arginine as well as Liquigen® (medium chain triglycerides), since the laboratory results were suggestive of protein malnutrition (see Table 1, first row of results showing unspecific lower values for several amino acids). The ensuing growth was satisfactory, but still not optimal. We titrated the protein supplement up to 4.2 g Protein/ kg/ day to where the serum amino acid profile had nearly normalized (see Table 1, 3rd row of results). We also added 1 g/kg/day of medium chain fatty acids (Liquigen®) to the milk. After a total of 4 weeks of this special diet we re-exposed the infant to the habitual diet of expressed BM enriched at a standard concentration of 4.2% FMS®. This time the infant tolerated the increased carbohydrates without any further hyperglycemic episodes and a more satisfactory weight gain. He was discharged at 2 ½ weeks corrected age (4 months chronological age) weighing 2930 g (Percentile 5), a body length of 48 cm (< P3) and a head circumference of 35 cm (P 25).

During the course of his stay the infant was supplemented with 800 IU of Vitamin D plus the extra vitamin D from the milk supplement. Thus, his daily dose averaged to 1000-1200 IU of Vitamin D. The alkaline phosphatase increased to twice the upper limit at 30 weeks corrected age. The serum ionized and total calcium as well as phosphate were always within the normal range. According to estimated urine losses, we adapted oral calcium-gluconate intake to a maximum of 0.6 mmol/kg/day and phosphate to a maximum of 0.5 mmol/kg/day. On discharge at 42 weeks corrected age, his alkaline phosphatase had normalized. On the chest x-ray film, performed to assess chronic lung disease at the age of 36 weeks, there was no evidence of osteopenia. We do not routinely perform DEXA scans to assess bone mass density.

Table 1

Analysis µmol/ L	Reference	29 4/7 weeks corrected age no special diet	30 4/7 weeks corrected age 1 week special diet	36 1/7 weeks corrected age 3 weeks normal diet
Taurine	30-340	35	49	51
Aspartic acid	5-50	13	13	10
Threonin	65-250	319	417	476
Serine	60-300	202	154	214
Asparagine	15-60	26	12	67
Glutamic acid	30-200	32	25	47
Glutamine	280-1000	146	81	872
Proline	140-330	117	108	262
Glycine	200-550	119	84	179
Alanine	130-500	172	144	384
Valine	80-210	103	114	108
Cysteine	25-80	13	15	31
Methionine	10-50	25	18	35
Isoleucine	30-80	29	38	52
Leucine	50-160	54	57	75
Tyrosine	45-140	181	273	140
Phenylalanine	3 0-110	57	86	52
Histidine	40-130	71	85	95
Tryptophan	20-70	25	37	41
Ornithine	40-210	38	46	116
Lysine	100-270	89	76	218
Arginine	20-120	14	15	64
Creatinine		36	33	31
Urea	mmol/L	0.8	1.6	3.3

6. Discussion

Breast milk (BM) for the neonate is unquestionably the ideal nutrition, specifically endorsed by the WHO to be the sole source of nutrition for the infant (newborn infant up to 6 months of age). BM has been proven to diminish sepsis and other infections, to reduce the incidence of necrotizing enterocolitis and even the rate of death. BM has also been shown to improve neuro-cognitive development, when compared to formula feeding (2, 3, 4, 5, 6).

In specific situations this source may be of insufficient energy and/or protein content, which is why a generic enrichment is typically added to expressed breast milk to enhance growth of the premature or growth restricted infant (4,7). Despite this enrichment, growth still remains suboptimal in many cases and certainly slower than in formula fed infants (2,7).

In our infant the course was complicated by a glucose intolerance. This is a phenomenon frequently observed in the extremely premature infant especially when intrauterine growth restriction is associated. It can occur in up to 50% of the very low birth weight infant (8, 9). It seems to be a multi-factorial transient disorder, clearly differentiated from transient neonatal diabetes, congenital diabetes, or even gram-negative or fungal sepsis. There were neither clinical signs nor laboratory results suggestive of the latter disorders in our infant.

The transient glucose intolerance seems to stem from intravenous glucose-overload in the presence of decreased insulin release in response to glucose as well as a failure of suppression of gluconeogenesis (9, 11)**.** In addition, the extremely premature infant will experience stress and critical illness, resulting in considerable release of pro-inflammatory cytokines, as well as the release of counter-regulatory hormones to insulin, such as cortisol and growth hormone. One of the clinical results of cytokine release is the development of chronic lung disease as seen in our infant. The glucose intolerance usually subsides within two weeks as the infant's endocrine system matures (8, 9).

The most widely used approach in the early phase of hyperglycemia is to restrict total glucose load, since early insulin infusion has not been shown to offer any substantial clinical benefit all the while putting the infant at risk of hypoglycemia (2, 8, 9, 10, 11) or even increase the rate of mortality as cited in the NIRTURE study (Neonatal Insuline Replacement Therapy in Europe) (10) . It is generally recommended not to go below a glucose load of 5-7 mg/kg/min, since the estimated requirements to maintain organ function (especially brain function) are around 6 mg/ kg/ minute. Only when this first measure does not lead to satisfactory glycemic controll, would a continuous insuline infusion be applied (10, 11). Once the infant is on such a treatment, glucose levels need to be monitored extra closely, leading to many blood draws and thus the potential of transfusion requirements, even when glucose is monitored continuously with an indwelling platinum probe.

In our case we were able to reduce the glucose load to within levels still satisfactory for organ function (i.e above 5mg/kg/min) without having to consider insulin therapy during the first two weeks of life, during which the infant still depended on intravenous nutrition.

Because of the recurrent hyperglycemic episodes our infant could only be enriched to 2.1% FMS (as opposed to 4.2%) at a total amount of 164 ml/kg/day, corresponding to

118 kcal/kg/day and approximately 2.3 g Protein/ kg/ day. At close to 4 weeks of age we were able to document a low serum urea and markedly reduced serum amino acids, especially the essential amino acids as well as glutamine, arginine and glycine (See Table 1, 1st row of results). In light of the growth restriction despite adequate caloric intake this was evidence for protein malnutrition. We then proceeded to enrich the milk with a specific amino acid powder (Nutricia Milupa UCD® 1 powder), which is a powdered medical food, indicated for the dietary management of all urea cycle disorders, containing a mixture of essential pure L-amino acids and enriched with vitamins, minerals and trace elements. Since this powder lacks arginine, and that arginine is a conditionally essential amino acid to the growing preterm infant, we also supplemented the milk with arginine at an amount of 0.05 mg/d. The total delivered protein amount was calculated at 3.9 g Protein/ kg/ day. The ensuing growth was satisfactory, but still not optimal. We titrated the protein supplement to 4.2 g Protein/ kg/ day to where the serum amino acid profile had nearly normalized (see Table 1, 3rd row of results). We also added 1 g/kg/day of medium chain fatty acids (Liquigen®) to the milk. After a total of 4 weeks of this special diet we re-exposed the infant to the habitual diet of expressed BM enriched at a standard concentration of 4.2% FMS®. This time he tolerated the glucose load without evidence of hyperglycemia. We assume that his endocrine system had matured enough as to where he could metabolize the ingested amount of glucose and that the special diet with the essential L-amino acids (especially Leucine) might have contributed to stimulate insulin secretion.

To our knowledge this is the first case to be documented in which an infant with glucose intolerance received an amino acid supplement to the expressed mother's BM to achieve better postnatal growth and to have the clinical effect confirmed by serum amino acid profiles, besides the anthropometric measures.

7. Learning Points

1) Even in light of correct caloric intake, there can still be a protein malnutrition with postnatal growth restriction.

2) Tailored enteral nutrition is feasible, but needs special attention to detail; for instance adding arginine to the specific amino acid powder (Nutricia Milupa UCD® 1 powder) and amino acid profiling to follow up effect of nutrional treatment.

3) Specific amino acid powder (Nutricia Milupa UCD® 1 powder) is poor in arginine and this specific amino acid is a conditionally essential amino acid for the growing human infant.

4) Protein malnutrition is probably far more prevalent than suspected in growth restricted infants and should be more actively sought and treated.

5) Glucose intolerance can be managed conservatively, if the glucose load is maintained above 5 mg/kg/min. before considering insulin infusion.

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