Amino acid and protein requirements in a preterm infant with classic phenylketonuria

D SHORTLAND, I SMITH, D E M FRANCIS, R ERSSER, AND O H WOLFF

Hospital for Sick Children, Great Ormond Street, London

SUMMARY A preterm infant with classic phenylketonuria required rather less than 90 mg/kg of phenylalanine and between 270 and 290 mg/kg tyrosine daily to achieve a rate of weight gain of around 20 g/kg per day. Using Lofenalac as the low phenylalanine food, the intake of tyrosine, an essential amino acid for patients with phenylketonuria seemed to be limiting in respect of growth.

In childhood, growth is the major determinant of protein requirement, which may be defined as the protein intake needed to maintain optimal growth and plasma amino acid concentrations. For preterm infants a guide to optimal growth and plasma amino acid concentrations is given by the average weight gain in utero^{1 2} (with allowance for catch up growth where appropriate) and the amino acid pattern in cord blood, which, apart from a fall in threonine and lysine after birth, closely resembles the pattern found in breast fed infants.³⁻⁴

Case report

A girl weighing 1.56 kg (10th centile; mother's height 3rd centile, father's height 10th centile) was born at 32 weeks' gestation by emergency caesarean section for reasons of pre-eclamptic toxæmia and antepartum haemorrhage. The neonatal course was uneventful except for a positive screening test for phenylketonuria. At age 13 days, her plasma phenylalanine concentration was 1879 µmol/l (31 mg/100 ml) and a low phenylalanine diet based upon Lofenalac (Mead Johnson) was introduced. Weight was 1.45 kg and length 41.1 cm (both below 10th centile).

Management of low phenylalanine diet

Nutrient intake was adjusted to achieve sustained catch up growth and was calculated using published figures for the composition of human milk,⁵ Gold Cap SMA (Wyeth Nutrition product information 1982), cows' milk⁵ and Lofenalac (Mead Johnson product information 1981). Frequent measurements were made of body weight, plasma amino acids, urea,

and electrolytes and less frequent measurements of length, plasma proteins, calcium, and phosphate. Changes in weight; in plasma phenylalanine and tyrosine; and in phenylalanine, tyrosine, and protein intake are summarised in Figs. 1, 2, and 3.

Before the diet the infant was receiving 235 ml/kg per day of pooled human milk providing an estimated protein intake of approximately 3 g/kg per day. Maximum weight gain was only 8.5 g/kg per day compared with an average fetal gain of 13 to 16 g/kg.^{1 2} Plasma concentrations of amino acids and urea were similar to those found in breast fed infants (tyrosine 78, methionine 34, cystine 72, taurine 122, threonine 275, arginine 107, valine 228, isoleucine 81, leucine 81, histidine 64, tryptophan 75, lysine 273 µmol/l, urea 2.4 mmol/l) indicating that amino acid intake was in balance with the slow rate of growth.

At the start of the diet the aim was to keep the energy, protein, and electrolyte intake in a similar range to that theoretically provided by pooled human milk. Lofenalac was given in an 8.3% solution with added glucose polymer and fat emulsion and combined with Gold Cap SMA in a quantity necessary to keep plasma phenylalanine

Fig. 1 Feeds from birth with resultant changes in protein, phenylalanine (Phe), and tyrosine (Tyr) intake.

Fig. 2 Weight gain of patient and 10th centile line for fetal and postnatal weights.²

A and B indicate points at which plasma tyrosine fell to lowest levels (29 and 33 $\mu\text{mol/l}$ (0.5 and 0.6 mg/100 ml)).

Fig. 3 Plasma phenylalanine and tyrosine concentrations.

*Phenylalanine 41 $\mu\text{mol/l}$ (0.02 mg/100 ml) and tyrosine 72 $\mu\text{mol/l}$ (1.3 mg/100 ml).⁴

concentrations in the therapeutic range of 180 to 480 $\mu\text{mol/l}$ (2.9 to 7.9 mg/100 ml).

The rate of weight gain increased immediately at the start of the diet and weight rose parallel to the 10th centile for a period of seven days. On a daily phenylalanine intake of 100 mg/kg and tyrosine intake of 170 mg/kg plasma phenylalanine fell to normal (lowest value 45 $\mu\text{mol/l}$ (0.7 mg/100 ml)) and plasma tyrosine fell step-wise to below normal (lowest value 29 $\mu\text{mol/l}$ (0.5 mg/100 ml)). On the day that the plasma tyrosine concentration was lowest,

and in the absence of any changes in nutritional intake, weight gain declined to the rate before the diet suggesting that tyrosine had become limiting for growth. The initial impression of a parallel relation between plasma tyrosine concentrations and weight gain were confirmed over the next few weeks. (Fig. 2). Only when the daily tyrosine intake was raised to between 270 and 290 mg/kg per day did plasma tyrosine concentrations rise to the normal range, and from this time on weight gain was over 20 g/kg/day until weight reached the 10th centile at 54 days of age. Changes in length followed the same pattern as changes in weight.

Lofenelac contains 54 mg of tyrosine per 16 g of nitrogen, a very similar proportion to that in SMA Gold Cap and a little more than is in cows' milk (48 mg/16 g nitrogen). To achieve a tyrosine intake of over 200 mg/kg per day it was necessary to increase the total protein intake to over 5 g/kg per day. To avoid an excessive fluid and energy intake this was eventually provided (Fig. 1) as a combination of cows' milk and Lofenelac. Despite the more rapid growth, plasma concentrations of urea and certain amino acids rose (methionine 130, valine 518, isoleucine 211 and histidine 163 $\mu\text{mol/l}$, urea 6.2 mmol/l), and cystine and taurine fell (45 and 49 $\mu\text{mol/l}$ respectively). Plasma electrolytes, calcium and phosphate values remained normal throughout. There was no evidence of hyponatraemia having contributed to slow growth.

Discussion

The poor growth recorded in the present patient when receiving pooled human milk is in accord with previous observations.^{6,7} An energy intake lower than theoretical estimates may have been the primary cause of the growth impairment and the prompt increase in the rate of weight gain on the diet, despite aiming to keep protein, energy, and mineral intake constant, supports this view. It should be emphasised, however, that simple addition of energy without protein, which is a common practice in special care units, could convert a balanced amino acid intake into one too low to sustain an increased rate of growth.

The rate of weight gain in our patient was closely linked to tyrosine intake and plasma tyrosine concentrations, suggesting that tyrosine intake was rate-limiting for growth. Tyrosine is an essential amino acid for children with phenylketonuria and Lofenelac contains only 54 mg of tyrosine/16 g of nitrogen (N), which is similar to the tyrosine content of Gold Cap SMA and lower than the tyrosine content of Minafen (65 mg/16 g N). Hence to achieve an optimal tyrosine intake for growth from

Lofenalac, it was necessary to increase total protein intake to over 5 g/kg/day. The amino acid imbalance which this caused was clearly related to the amino acid pattern of the feeds since both cows' milk and Lofenalac are low in cystine and taurine and relatively high in methionine and branched-chain amino acids. We suggest that the tyrosine content of Lofenalac should be increased by at least 20% to enable it to be used with whey based milks, thus avoiding an unnecessarily high protein intake and unbalanced amino acid intake.

The data presented here show that when our patient was growing at 20 g/kg/per day, which was necessary to achieve catch up growth, she required rather less than 90 mg/kg of phenylalanine and between 270 and 290 mg/kg of tyrosine. In infants without phenylketonuria, who are able to convert phenylalanine to tyrosine, the requirements for these two amino acids are best considered together. We conclude that a combined intake of at least 350 mg/kg, necessitating a protein intake of 3.5 to 4 g/kg from a whey adapted milk, is required for catch up growth in preterm infants. This estimate is in agreement with other studies.^{6,7} It has been pointed out that the volumes of milks such as Gold Cap SMA needed to achieve such protein intakes are needlessly high and could be avoided by using milks of higher protein content. We would add that the energy intake provided by large volumes of SMA is

also high and may lead to reluctance to feed (and therefore prolonged tube feeding) and excessive fat deposition.

We thank Dr Gerald McEnery for referring this patient to us and for providing details of the first two weeks of life. Dr Smith is in receipt of financial support from the Medical Research Council.

References

- Shaw JCL. Parenteral nutrition in the management of sick low birth weight infants. *Pediatr Clin North Am* 1973;**20**:333-58.
- Gairdner D, Pearson J. *Growth and development chart*. Hertford: Castlemead Publications, 1971.
- Pohlandt F. Plasma amino acid concentrations in umbilical cord vein and artery of newborn infants after elective cesarean section or spontaneous delivery. *J Pediatr* 1978;**92**:617-23.
- Pohlandt F. Plasma amino acid concentrations in newborn infants breast fed ad libitum. *J Pediatr* 1978;**92**:614-6.
- Paul AA, Southgate DAT, Russell J, comps. Amino acid composition (mg/100 g food) and fatty acid composition (g/100 g food). *First supplement to McCance and Widdowson's The composition of foods*. London: HMSO Ministry of Agriculture, Fisheries and Food MRF, 1980.
- French TJ, Colbeck M, Burman D, Speidel BD, Hendey RA. A modified cows' milk formula suitable for low birthweight infants. *Arch Dis Child*. 1982;**57**:507-10.
- Brooke OG, Wood C, Barley J. Energy balance, nitrogen balance, and growth in preterm infants fed expressed breast milk, a premature infant formula, and two low-solute adapted formulae. *Arch Dis Child* 1982;**57**:898-904.

Correspondence to Dr I Smith, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Received 29 October 1984

Fatal hepatitis B in infant born to a HBsAg carrier with HBsAb

C I EWING AND D C DAVIDSON

Alder Hey Children's Hospital, Liverpool

SUMMARY Fulminant hepatic failure occurred in an 11 week old baby of a Caucasian mother who was hepatitis B surface antigen positive, B e antigen negative, and B e antibody positive. Infants of hepatitis B e antigen positive mothers receive immunoprophylaxis against hepatitis, unlike those born to mothers who are B e antibody positive.

Case history

The baby was admitted to hospital at 10 weeks of age having become jaundiced over a 24 hour period. She was passing dark urine and pale stools. She had been born after a normal delivery at 36 weeks' gestation, and weighed 2.5 kg. Apart from an

episode of transient tachypnoea during the first 48 hours of life, the neonatal period was uneventful. Both parents were Caucasian, there was no history of contact with blood products or drug addiction, and the mother had remained well throughout her pregnancy. The baby had not been exposed to hepatitis nor had she received any blood transfusions.

On examination she was pale and slightly icteric. Investigations showed blood sugar 1.3 mmol/l (23.4 mg/100 ml); prothrombin time greater than 90 seconds (control 11.5 seconds); kaolin cephalin time greater than 3 minutes (control 42 seconds); haemoglobin 9.8 g/dl, reticulocytes 5%, fibrinogen nil detected; total serum bilirubin 268 mmol/l (15.7 mg/100 ml) (all unconjugated); alkaline phosphatase 170 KA units %, aspartate transaminase 113 IU/l,