Dietetic Management of a Preterm Infant with Nephrogenic Diabetes Insipidus


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Background

An extremely low birth weight (ELBW) preterm male infant, Baby C*, born 27 weeks and weighing 880 g via emergency caesarean section following maternal placental abruption. He was born in poor condition and required ventilator support (Bilevel Positive Airway Pressure [BiPAP]/continuous positive airway pressure [CPAP]) for the first 34 days of life. He had a strong family background of nephrogenic diabetes insipidus and was diagnosed via genetic analysis. Extensive dietetic support was provided jointly by the neonatal dietitian at the Broomfield Hospital and the paediatric renal dietitian at Great Ormond Street Hospital (GOSH), in order to optimise growth while preserving renal function. Baby C stayed on the neonatal unit for 82 days before being discharged home.

Prematurity

Preterm infants are defined as babies born before 37 weeks of pregnancy are completed. According to the Office of National Statistics (2017), about 54,000 or 8% of live births in the UK were preterm.[1] Prematurity, depending on the infant's birth gestation, presents an increased risk of long-term illness and disability. Optimisation of nutrition provision is vital, as the rate of growth, or growth velocity during the time spent in the neonatal unit influences cognitive and growth outcomes of ELBW premature infants.[2]

Nephrogenic diabetes insipidus in the pre-term infant

Maintenance of water and electrolyte homeostasis includes appropriate concentration of urine, which is regulated via arginine vasopressin (AVP), the antidiuretic hormone. Congenital nephrogenic diabetes insipidus (NDI) is a rare genetic disorder characterised by the kidney failing to respond to arginine vasopressin.[3] This leads to the kidney being unable to concentrate urine through reabsorption of water in the renal tubular collecting ducts. NDI differs from central diabetes insipidus in which the brain fails to produce AVP. Most cases of NDI are caused by X-linked mutations and therefore more boys than girls are affected.[3] The incidence of NDI is unknown, but it is estimated to affect 4 in every 1,000,000 males with the X-linked recessive gene.[4] Infants with NDI present with polyuria and polydipsia, which can rapidly lead to dehydration, hypernatremia and faltering growth if fluid intake is insufficient.

A high-water intake is required to ensure that children with NDI can excrete a normal renal solute load (RSL) – all solutes which require excretion by the kidneys.[5] Infants with NDI have a preference for water which can displace the amount of breast milk or formula they drink.[3] This can lead to faltering growth which is further exacerbated by a commonly associated symptom of vomiting.[3] The protein requirements of the preterm infant are greater than the term infant, so protein intake should be considered, as a higher intake of this will increase the RSL.

Management of NDI includes ensuring an adequate fluid intake. The usual aim for the RSL of a feed is approximately 15 mOsm/kg H_2O/kg body weight. However, <20 mOsm/kg H_2O/kg body weight is usually accepted, particularly in situations where growth is challenging. The RSL is calculated using the formula from Fomon & Ziegler[5] as below:

4 x total g protein + 2 (Na mmol + K mmol)/kg body weight

Combined with drug treatment, which includes a diuretic, e.g. chlorothiazide and a non-steroidal anti-inflammatory drug e.g. indomethacin, the volume required for urine output can be reduced. However, initiation of drug treatment in the premature infant with NDI is not common due to the risk of gastrointestinal complications, including necrotising enterocoliti[3] and, hence, it was not initially used on Baby C.

This case study will demonstrate the challenges of meeting nutritional requirements whilst trying to prevent dehydration.

Dietetic interventions

Week 1: Due to his prematurity, birthweight and subsequently low body stores, Baby C was initiated on parenteral nutrition (PN) on Day 1 as per the East of England neonatal parenteral feeding guidelines. Trophic feeding on mother's expressed breast milk (EBM) was also commenced via orogastric tube, at 1 ml/kg/hour to help with gut maturation. By Day 2, it was clear that there were issues physiologically, as he developed hyperglycaemia, polyuria and hypernatraemia.

See **Figure 1** for the trend in plasma sodium levels. NDI was suspected due to family history. Due to the intricacies involved in keeping RSL in check to prevent polyuria and renal profile abnormalities, the medical decision made was to significantly reduce protein, sodium and potassium provision. Unfortunately, this resulted in not being able to meet Baby C's requirements for growth, as protein, sodium and potassium are all essential components of adequate preterm growth but can be problematic with NDI management.

Weeks 2-5: Genetic tests confirmed a diagnosis of NDI at Day 20 of life (corrected gestational age of 29 weeks and 5 days) as the patient was found to be hemizygous for the familial c.262G>A p[Val88Met] pathogenic variant in the *AVPR2* gene. At this point, hypernatremia, hyperkalaemia and uraemia were daily issues. PN continued, with minimal progression with enteral feeds. The GOSH renal team advised to reduce provision of protein and sodium to try and alleviate physiological abnormalities from NDI. Protein provision dropped to about 1.4 g/kg (40% minimum requirements) and sodium 1 mmol/kg (50% minimum requirements). Plasma urea is often a useful marker to indicate adequate protein intake in neonates, however fluctuations in hydration status meant that it could not be used for this purpose (see **Figure 2**).

Tolerance of EBM started improving from about Day 24 and PN weaned off completely by Day 35 (corrected gestation 31 weeks and 6 days) to a combination of EBM, 5% Maxijul solution and 5% IV dextrose, providing an estimated 245 ml/kg, 124 kcal/kg, 1.65 g protein/kg, 1.16 mmol sodium/kg and 2.46 mmol potassium/kg in 24 hours. His urine output was estimated at 7.61 ml/kg/hour. While energy needs were met via the addition of glucose polymer and IV fluids, protein (47%) and sodium (58%) provision were inadequate to meet minimum requirements for growth. Close communication with the GOSH renal dietitians was ongoing with regards to optimal nutritional management for Baby C. Due to his prematurity, a RSL of 15 mOsm/kg H_2O/kg body weight would not, from a neonatal point of view, provide adequate protein, sodium and potassium for optimal growth of 15-20 g/kg/day.[6,7] His weight had dropped from 9th-25th centile at birth to 0.4th-2nd centile by Day 34 of life (see **Figure 3** for his growth chart). Preterm infants of Baby C's gestation and weight often require fortification of mother's own milk to help achieve optimum nutritional intake, particularly with regards to protein, fat soluble vitamins, sodium, potassium and other micronutrients. A commercial powdered preparation is used by the Broomfield Neonatal Unit, whereby a 1 g sachet of breast milk fortifier is added to 25 ml expressed breast milk, if given according to the manufacturer's instructions. On Day 41, the decision was taken to fortify maternal breast milk. However, as we were also aiming to limit RSL, maternal breast milk for Baby C could only be fortified up to 1/3 strength (1 g sachet to 75 ml EBM). Fortunately, because of his high fluid requirements, EBM was given at 180 ml/kg, which resulted in the provision of an estimated 3 g/kg protein, 2.4 mmol/kg sodium, 3.53 mmol/kg potassium and an RSL of 21 mOsm/kg H_2O/kg body weight. Fluid provision at this stage ranged from 200-260 ml/kg. The feeding plan was tolerated well.

Figure 1: Sodium

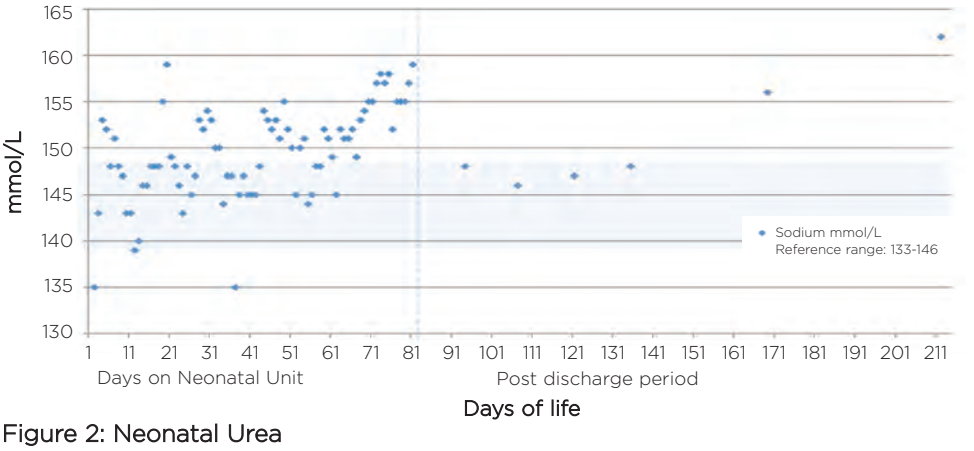
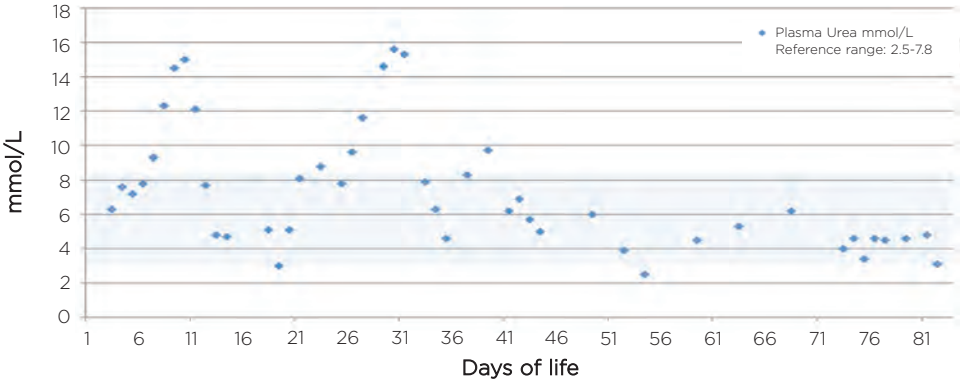


Figure 2: Neonatal Urea



Weeks 6-10: Maternal breast milk supplies reduced significantly, and on Day 45, feeds were changed to 120 ml/kg 'first' infant formula and 80 ml/kg high energy formula, with top ups of water to 50 ml/kg (RSL 22 mOsm/kg H_2O/kg body weight). The calorie load with this feeding plan was high, at about 160 kcal/kg, which was approximately 20% higher than Baby C's estimated energy requirements. Although this contributed to a much quicker weight gain, averaging >22 g/kg/day, it was of concern that the excessive calorie intake would contribute to higher fat accretion compared to protein deposition. Although preterm infants often require catch-up growth, rapid weight gain, potentially contributing to the increased risk of obesity in later life, is an undesirable outcome in preterm nutritional management.[8] Another concern was that the protein:energy ratio was low on this feeding plan.

At Day 60, Baby C's feed was changed to a formula designed for premature infants at 180 ml/kg plus free water top ups to 270 ml/kg, to reduce calorie load and enhance the protein:energy ratio. Growth velocity adjusted to a more acceptable 18 g/kg/day. RSL, however, was at 27.4 mOsm/kg H_2O/kg body weight. Plasma sodium levels also gradually increased, to a peak of 157 mmol/L on Day 76. Baby C's fluid intake was therefore increased to 310 ml/kg.

Week 10: At Day 76, Baby C reached term age (corrected gestation 37 weeks and 5 days), which meant his sodium requirements were theoretically lower. Feeds were changed to 'first' infant formula at 180 ml/kg and 130 ml/kg free water, in the hope of reducing sodium levels. RSL was now approximately 18 mOsm/kg H_2O/kg body weight. His weight was 2.16 kg, which continued to track the 0.4th-2nd centile. Urine output remained high at >10 ml/kg/hr. Plans were made to transfer him to his local hospital to prepare for community follow up and future medical care under the paediatric renal team at GOSH.

Follow up

Baby C had his first GOSH outpatient appointment when he reached term corrected gestational age (approximately 40 weeks corrected). Baby C was taking total fluids of 310 ml/kg consisting 180 ml/kg 'first' infant formula and 130 ml/kg water as 3 hourly bolus feeds. His intake was approximately 115 kcal/kg and 2.3 g/kg protein, with an RSL of 17 mOsm/kg H_2O/kg body weight. He commenced on thiazide and ibuprofen medication for his NDI.

At 2-6 weeks corrected gestational age, Baby C developed an inguinal hernia and projectile vomiting. His water volume was reduced in liaison with the medical team to see if it would help vomiting, and the feeding plan was amended to administer his feeds via the pump. He was then on 190 ml/kg 'first' infant formula and 30 ml/kg water, with an additional 3% glucose polymer. RSL was 17.1 mOsm/kg H_2O/kg body weight. At 6-12 weeks the feeding plan was changed to 190 ml/kg formula, with glucose polymer providing 210 kcal/kg and 2.5 g/kg protein, with an RSL of 20 mOsm/kg H_2O/kg body weight. Baby C was pulling his nasogastric tube out regularly and listed for a gastrostomy at 7 weeks. A gastrostomy was eventually inserted at 23 weeks gestational age, as previous dates had to be cancelled due to intercurrent illnesses. Since the write up of the article, Baby C's growth remains below the 0.4th centile but the rate of growth is good, and weight and length parameters are proportional.

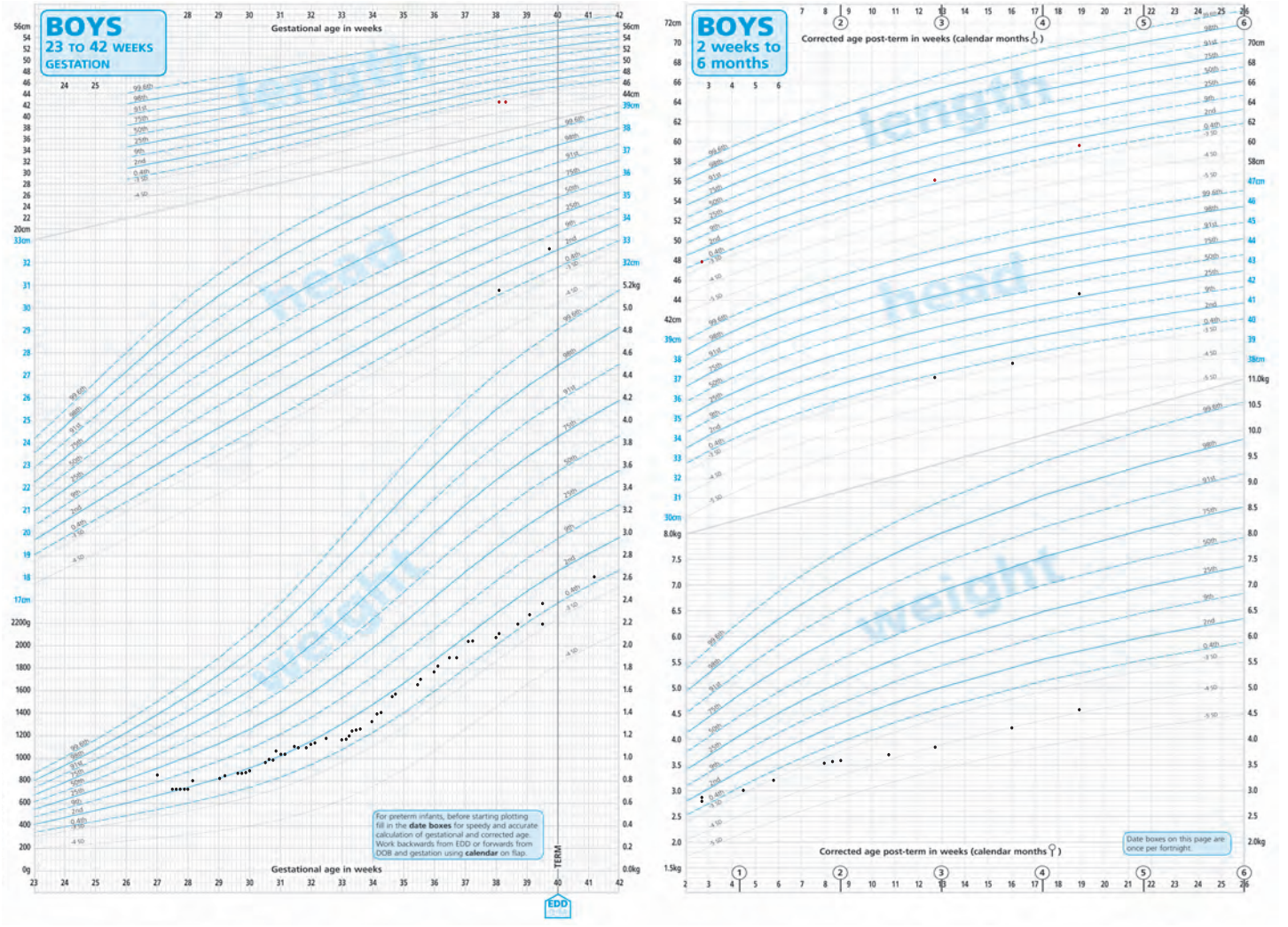
Discussion

The aim of initial dietetic management was to consider a feed with a reasonable solute load whilst aiming for minimum energy and protein requirements for preterm growth. Feeding on a RSL of 15 mOsm/kg H_2O/kg body weight would have required a fluid intake of >200 ml/kg body weight for excretion; however, it was a challenge keeping within these limits due to the need to meet the increased protein and electrolyte needs of Baby C. On the other hand, raising provision would heighten urine production. However, the theory now developing is that if electrolytes are needed to be incorporated into the cells, then they will not need to be excreted in the urine and, therefore, they would not contribute to the RSL. The collaboration of the multidisciplinary team is vital to ensure that the clinical context is viewed correctly.

Conclusion

As far as we are aware, this is the second documented case involving a preterm infant with NDI, and the youngest. Serious challenges with regards to facilitating adequate growth while preserving renal function were posed to the dietitians and medical teams involved. This case strongly showcases the high value contribution which dietitians can provide and demonstrates the need for close collaboration between two niche areas of paediatric dietetics with very specific nutritional objectives.

Figure 3: Growth Charts



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*Patient name changed to protect patient confidentiality.