

Original Articles

Central Diabetes Insipidus in Premature Neonates with Brain Injury

LTW CHAN, VYH YU

Abstract

We report two premature infants with respiratory distress syndrome who developed central diabetes insipidus following intracranial insult. There was no midline defect noted both radiologically and clinically. Pituitary hormone profiles were within normal limits in the infants. Intranasal desmopressin was prescribed to both of them with prompt response which was shown by a reduction of urine output and normalization of serum sodium level with urine concentrating ability. The dose and administration method of desmopressin were repeatedly adjusted. Central diabetes insipidus did not resolve even after the complete resolution of intraventricular haemorrhage in one of the babies.

Key words

Central diabetes insipidus; Desmopressin

Central diabetes insipidus is rare in the neonatal period. It has been reported in infants with meningitis caused by group B Streptococcus, listeria, congenital viral infection including toxoplasmosis and cytomegalovirus, central nervous system malformation like holoprosencephaly and septo-optic dysplasia, chromosomal abnormality, intraventricular haemorrhage, and hypoxic ischaemic encephalopathy.¹⁻⁷ Vasopressin has been used successfully in treating diabetes insipidus in neonates in the form of intranasal, oral, subcutaneous or intravenous preparations.^{1,4,8,9} The following report describes two premature infants with respiratory distress syndrome. One of them suffered from intraventricular haemorrhage who developed central diabetes insipidus on day 3 of life, and the other was born asphyxiated resulting in periventricular leukomalacia. Both were successfully treated with intranasal desmopressin spray. Unlike a previous report on a baby with diabetes insipidus after intraventricular haemorrhage,¹ the first case had persistent central diabetes

insipidus even with complete resolution of the intracranial bleed.

Case Reports

Case 1

A 25-week gestation male infant weighing 976 g was born at the level 2 nursery of Dandenong Hospital in Victoria, Australia. His apgar scores were 3 in one minute and 8 at five minutes, for which active resuscitation was required including positive pressure ventilation, external cardiac massage, adrenaline injection, and fluid resuscitation. He was then transferred to Monash Medical Centre which is a tertiary Neonatal Intensive Care Unit centre by the Neonatal Emergency Transport Service team (NETS).

On admission, the infant was not dysmorphic and his first blood gas showed metabolic acidosis with pH 7.16 and base deficit of 15 mmol/L. Chest x-ray revealed respiratory distress syndrome and surfactant treatment was given via endotracheal tube. His mean arterial blood pressure was low on day 1 which required fluid resuscitation and inotropic support with dopamine up to 15 microgram/kg/min. His condition was further complicated by coagulopathy with prolonged International Normalization Ratio and Partial Thromboplastin Time which required Vitamin K injection as well as Fresh Frozen Plasma transfusion. Cranial ultrasound on day 5 confirmed bilateral grade 2 intraventricular haemorrhage without other structural abnormality seen.

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By day 3, hypernatraemia (158 mmol/L) was noted which were thought to be related to his excessive water loss from skin despite the use of high ambient humidity of 80%. Hence fluid replacement of up to 225 ml/kg/day was prescribed. Hypernatraemia was corrected by this increase in infusion rate and the serum sodium over this period ranged from 145 to 156 mmol/L on a maintenance sodium intake of 3 mmol/day as part of his parenteral nutrition. Blood sugar level had been stable and his urea levels ranged from 2.9 to 11.6 mmol/L on an amino acid intake of 3.5 g/kg/day. Serum calcium and potassium were within normal ranges. It was noted even as early as day 3 that he had polyuria of 12.5 ml/kg/hr (Figure 1). Otherwise, his renal function was normal and there was no glycosuria. The possibility of diabetes insipidus was suspected as he continued to pass large amounts of urine. Serum and urine osmolality of 326 mOsm/kg and 174 mOsm/kg respectively were demonstrated. Repeated measurements still revealed simultaneous hypotonic urine with high serum osmolality.

On day 14, desmopressin (DDAVP) was given as a diagnostic test and as a therapeutic trial. A dose of 5 micrograms was given intranasally, resulted in a marked reduction of urine output over the next 24 hours (Figure 2). Serum sodium dropped to 120 mmol/L with serum and urine osmolality of 260 and 485 mOsm/kg respectively

24 hours after the dose. Based on these findings, the diagnosis of central diabetes insipidus was made in view of normal renal function and electrolytes to account for his polyuria. Desmopressin therapy was continued and 4 hourly monitoring of urine output and daily urine osmolality revealed a prompt reduction in urine output and increase in urine osmolality following administration. Drug dosage was repeatedly adjusted and titrated according to the clinical and biochemical parameters. Subsequently he was put on DDAVP nasal spray of 0.25 microgram 8 hourly. This spray form was prepared by the hospital pharmacy department in view of a poor response with the droplet form which might have caused erratic and poor absorption from the nasal mucosa.

Endocrine investigations performed revealed a normal serum Thyroid Stimulating Hormone (TSH) (2.81 mU/L) and appropriate Growth Hormone (GH) (13.1 mU/L), Luteinizing Hormone (LH) (4.3 IU/L) as well as Follicle Stimulating Hormone (FSH) (3.4 IU/L) levels. Repeated cranial ultrasounds demonstrated resolution of the haemorrhage and complete resorption of blood with normal ventricular size. The infant also recovered from hyaline membrane disease which required assisted ventilation for 26 days. Consequently, he developed chronic lung disease requiring low flow oxygen therapy. Central diabetes insipidus persisted and the infant

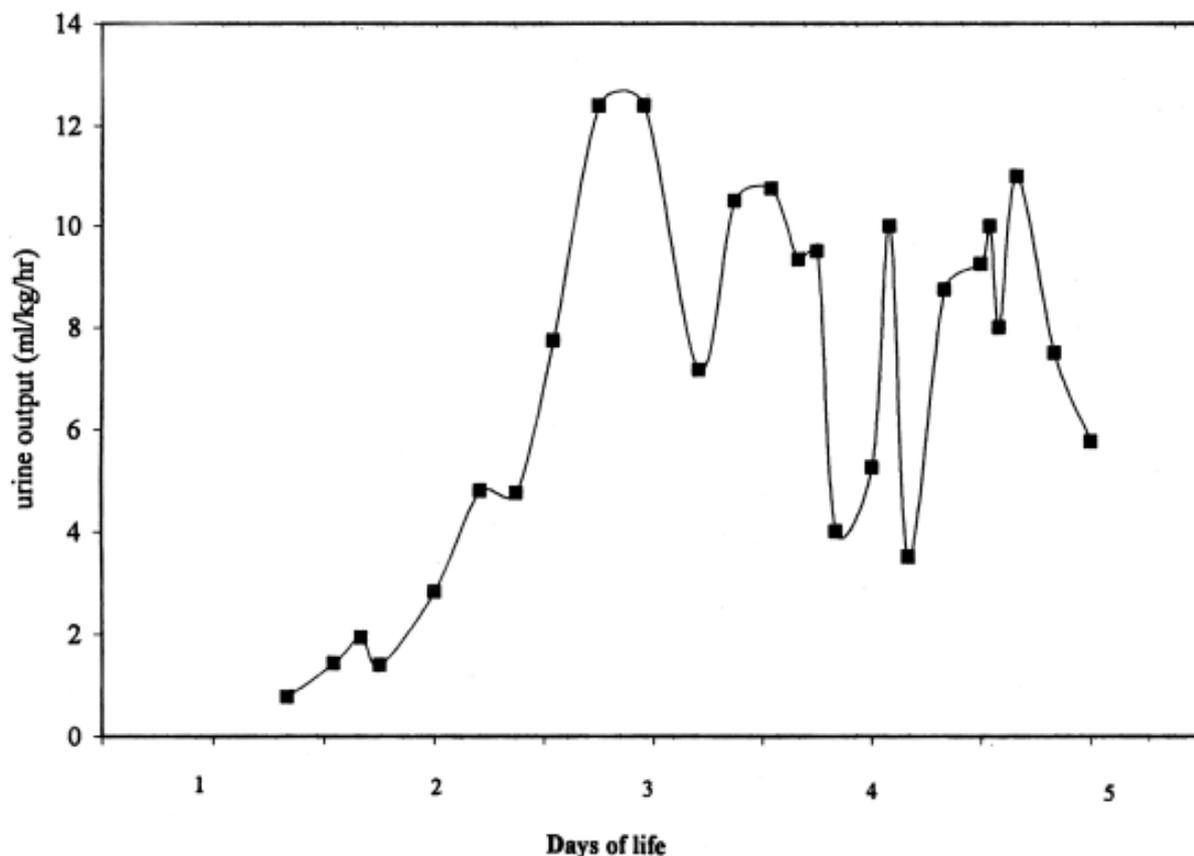


Figure 1 Urine output in the first four days of life

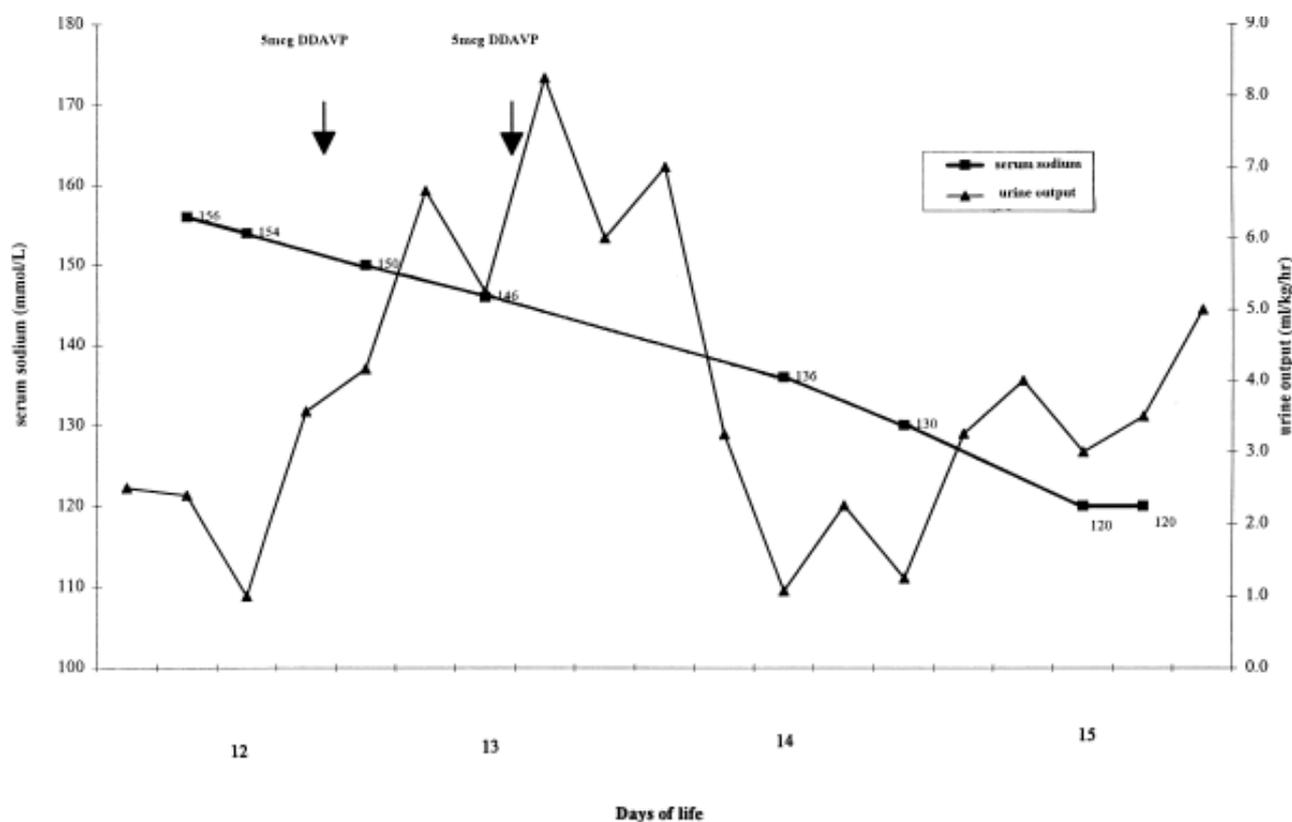


Figure 2 Serum sodium and urine output changes in response to DDAVP

remained in DDAVP at term (age of three months) when this report was written.

Case 2

A 25-week gestation female was born by vaginal breech delivery also in Dandenong Hospital with a birth weight of 791 grams. The infant was asphyxiated at birth with apgar scores of 2 in one minute and 2 in five minutes, for which active resuscitation was required including positive ventilation and external cardiac massage. Initial arterial blood gas showed a pH of 6.93 with base deficit of 22 mmol/L. She soon developed frank seizures with twitching of limbs at around one hour of age which was treated by a total of 30 miligram/kg of phenobarbitone. Seizures eventually stopped at five hours of age and she was transferred to Monash Medical Centre by NETS.

She experienced severe hypotension secondary to myocardial dysfunction which was confirmed by echocardiogram during the first day of life. Dopamine, dobutamine and adrenaline infusions were prescribed at their maximum doses of 30 microgram/kg/min, 30 microgram/kg/min and 0.4 microgram/kg/min respectively, for a total of six days. Intravenous hydrocortisone injection at a six hourly dose of 2 miligram/kg/dose was also added for the hypotension. Her course was further complicated by acute tubular necrosis (ATN) with oliguria, metabolic acidosis and a rising blood urea

(maximum 13.1 mmol/L) and serum creatinine (maximum 115 umol/L). Because of persistent hyperkalaemia (maximum 7.1 mmol/L), she developed episodes of arrhythmia with bradycardia (2:1 heart block) and even ventricular tachycardia which required external cardiac massage followed by therapy with glucose-insulin, calcium and resonium. Her condition gradually stabilised after conservative treatment and her urine output as well as renal function improved from day 3 of life.

Her serum sodium level progressively increased from day 3 onwards, which was attributed to excessive water loss from the skin. Hence total daily fluid intake was increased to 180 ml/kg/day which was followed by a concomitant drop in serum sodium from 165 mmol/L on day 4 to below 150 mmol/L on day 6 on a maintenance sodium input of 3 mmol/kg/day as part of her parenteral nutrition. Blood sugar level has been stable and her serum urea levels ranged from 4.8 to 13.1 mmol/L on an amino acid intake of 1.8 g/kg/day. Her serum sodium level was controlled at a reasonable level in the following week with a total fluid intake of 200 to 220 ml/kg/day.

However, it was noted that she was markedly polyuric on day 12 with average daily urine output of 11.4 ml/kg/hr, initially considered to be the result of ATN secondary to perinatal asphyxia. Nevertheless the possibility of central diabetes insipidus was suspected as the serum sodium was at the range of 143 to 151 mmol/L with

polyuria of 6.9 to 8.0 ml/kg/hr in view of a normalized renal function as well as serum potassium and calcium levels. Serum and urine osmolalities were shown to be 313 mOsm/kg and 160 mOsm/kg respectively on day 15 with a serum sodium of 151 mmol/L. Intranasal DDAVP was prescribed at a dose of 0.12 microgram/kg/dose resulting in a decrease in urine output from 10.3 ml/kg/hr to 4.8 ml/kg/hr in a 12-hour period on day 16. Urine osmolality was increased to 367 mOsm/kg six hours after the dose of DDAVP. DDAVP dose was repeatedly adjusted and she was receiving a dose of 0.2 microgram/kg/dose 12 hourly with a satisfactory control in serum sodium levels and an average daily urine output of 5.5 ml/kg/hr on a total daily fluid intake of 160 ml/kg/day at the time when this report was written (age of one month).

Cranial ultrasound examination on day 2 revealed increased echogenicity in the periventricular white matter in the parieto-occipital regions which was suggestive of ischaemia. Repeated examination confirmed the presence of periventricular leukomalacia without cyst formation. Renal ultrasound was unremarkable. Pituitary hormonal files showed TSH 4.24 mU/L, LH <0.5 IU/L, FSH 1.4 IU/L, and spot cortisol 182 nmol/L.

Discussion

Although central diabetes insipidus is rare, it is increasingly recognized in the newborn.¹⁰ Clinically the condition is characterised by excessive fluid output and intake. Diagnosis is difficult in the premature newborn because an excessive urine output is easily overlooked and the high serum sodium is usually ascribed to the marked body water loss from skin. Full term infants may present late with non-specific symptoms such as anorexia, vomiting, poor weight gain, constipation or retarded development. The diagnoses in our infants were confirmed by failure to concentrate the urine despite high serum osmolality and reversal by administration of vasopressin or an analogue. A classical water deprivation test was considered hazardous in a critically ill neonate although it was reported to have been done in those full term infants. Assays for plasma and urine vasopressin are available in some centres. Polyuria due to hypercalcaemia or hypokalaemia has to be excluded and allowance made for the lesser concentration power of the neonatal kidney. However, from our results, it was shown that the kidneys of premature infant could concentrate his urine up to 700 mOsm/kg. Nephrogenic diabetes insipidus is a differential diagnosis, in which there would have been a failure to respond to desmopressin. Therefore one should be alert to the possibility of central diabetes insipidus in a baby with high serum sodium and an excessive amount of urine.

The traditional treatment of central diabetes insipidus

involves the replacement of vasopressin or use of an analogue, the most effective available being desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin), which is more potent than the native molecule and has a five times longer half-life. The solution is given by nasal instillation. The duration of antidiuretic action of desmopressin has been shown to be 10 hours to 20 hours. A suitable starting dose has been suggested to be 5 to 10 micrograms once or twice daily.¹⁰ A different drug dose of 0.4 microgram/kg was suggested in a case report on a baby with chromosomal abnormality while a daily dose of 1 microgram was prescribed to a premature infant of 1.2 kg with transient diabetes insipidus secondary to intraventricular haemorrhage.^{1,7} Our first infant received a starting dose of 5 micrograms which resulted in a marked reduction of urine output and hyponatraemia of 120 mmol/L 24 hours after the treatment dose. Repeated adjustments were needed before titrating to the current eight hourly dose of 0.2 microgram DDAVP to this 2 kilogram baby. The second infant received a 12 hourly dose of 0.2 microgram/kg/dose of DDAVP with a satisfactory control of biochemical parameters. We therefore advise a careful and conservative approach to start at a low dose of DDAVP at 0.1 microgram/kg/dose 12 hourly as the large fluctuation in serum sodium levels which was noted in our first infant might be harmful to the brain.

The usual preparation of DDAVP is in a solution form measured out in a small plastic tube graduated in fixed volume increments and given by nasal instillation. We encountered erratic absorption in our first patient especially when he was on nasal continuous positive airway pressure (CPAP) therapy for his ongoing lung problem. The positive pressure produced may affect the delivery and absorption of the drug. This was avoided by suspending the CPAP ventilation while instilling the drug through the nose. However, drug delivery to the baby was still erratic even as the above-mentioned measures were followed. There was variable urine output after each DDAVP dose. Subsequently this problem was overcome by changing the nasal instillation to nasal spray which was also used in our second baby. The spray form is also more easily managed by the parents when the baby is discharged home.

A previous case report on a premature infant with central diabetes insipidus secondary to intraventricular haemorrhage had a transient course which was attributable to the cerebral oedema following intraventricular haemorrhage.¹ For patients with underlying causes such as infection or intracranial abnormalities, their metabolic problem could be life-long. Permanent severe pituitary diabetes insipidus occurs only with destruction of the supraoptic nucleus or high stalk section, more distal lesions usually causing only transient partial malfunction.¹⁰ Our two infants did not have a positive family history suggesting the rare familial disorders nor did they

demonstrate any evidence of intracranial abnormality, central nervous system infection or head trauma.¹¹ The hormonal deficiency of the hypothalamic-pituitary glands appeared to be highly selective, as the adrenal and thyroid axes were largely unaffected. Therefore, we speculate that diabetes insipidus following intraventricular haemorrhage or ischaemic damage is not necessarily transient in nature, its duration depends on the location of damage in the pituitary glands. MRI brain should be done later in infancy if diabetes insipidus persists.

In summary, we report two premature infants with central diabetes insipidus following intraventricular haemorrhage and periventricular leukomalacia secondary to asphyxia who were both successfully treated by nasal spray of desmopressin. The diagnosis of diabetes insipidus in premature infants may be delayed because of the common occurrence of high serum sodium levels in the first few days of life secondary to excessive transcutaneous water loss. Structural intracranial abnormalities and central nervous system infections have to be ruled out. The dose of DDAVP should be started at a low dose and titrated according to biochemical parameters and urine output. Desmopressin therapy is not without side effect as it may cause large fluctuation in serum sodium levels which are potentially harmful to the brain.

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