Case Reports Journal

ISSN: 2574-0814
Case Rep J. 2018;2(1):010
Case Report | Open Access

A Case of Neonatal Central Diabetes Insipidus in a Premature Infant – Challenges in Diagnosis and Management

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Rec: October 04, 2017; **Acc:** February 19, 2018; **Pub:** February 28, 2018

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Abstract

Background: Neonatal central diabetes insipidus (CDI) has been associated with meningitis, central nervous system malformations, intraventricular hemorrhage and hypoxic ischemic encephalopathy.

Case report: A 25 week premature male neonate with a birth weight of 804 grams had a stormy perinatal clinical course complicated by grade III bilateral intraventricular hemorrhage. On 69th day of life, he developed polyuria with a serum sodium of 157 mmol/L, serum osmolality of 352 mmol/kg and a urine osmolality of 181 mmol/kg, which was diagnostic of diabetes insipidus. Intravenous (IV) vasopressin was commenced at 0.1 mU/kg/h and titrated upwards to effect. He showed a gradual response over the next 72 h with a decrease in serum sodium to 133 mmol/L and serum osmolality to 269 mmol/kg and an increase in urine osmolality to 291 mmol/kg.

Discussion: To our knowledge, this is the first report of IV vasopressin in the diagnosis of CDI. Other studies have used intranasal desmopressin which has been associated with large swings in serum sodium. The advantage with the initial use of an IV vasopressin infusion lies in the titration of the dose in a controlled and safe manner to establish response.

Introduction

Diabetes insipidus (DI) is a disorder of water homeostasis characterized by failure to concentrate urine due to inadequate production of vasopressin, also known as central diabetes insipidus (CDI), or due to resistance of the tubules to the effects of antidiuretic hormone which results in nephrogenic diabetes insipidus (NDI) [1].

The neonate has a relatively large body surface area which increases the insensible water loss. Moreover, their kidneys are not fully mature yet and there may be a high urine output coupled with the reduced ability to excrete sodium. These are risk factors for the neonate to develop hypernatremic dehydration, associated with elevated serum sodium levels [2]. However, persistent hypernatremia in the neonate despite increased fluid intake should alert the clinician to the possible diagnosis of DI.

Case Report

A baby boy was delivered prematurely at 25 weeks gestation by a normal vaginal delivery, with a birth weight of 804 grams. The Apgar score was 2 at 1 minute and 7 at 10 minutes of life. He is the first child of a non-consanguineous marriage.

His clinical course was complicated by severe respiratory distress syndrome requiring 3 doses of surfactant and mechanical ventilation for 70 days, with non-invasive positive pressure ventilation for another 26 days. Of significance, he developed grade 3 bilateral intraventricular hemorrhage with stable ventriculomegaly and *Enterococcus faecalis* sepsis with acute kidney injury.

Significant hypernatremia was noticed on 69th day of life at 34+4 weeks postmenstrual age, which was associated with polyuria of 6 ml per kg per hour. The serum and urine biochemistry were diagnostic of DI, with a serum sodium level of 157 mmol/L, an elevated serum osmolality of 352 mmol/kg with a concomitant low urine osmolality of 181 mmol/kg and a urine sodium level of 67 mmol/L. He was initially managed with free water replacement but only demonstrated a partial response, achieving a serum sodium level of 148 mmol/L to 152 mmol/L, while on a total fluid intake of 170 ml per kg per day.

A trial of intravenous vasopressin was then instituted. Free water replacement was stopped prior to the commencement of vasopressin. The preparation of the intravenous vasopressin infusion was challenging, as it required a dilution in 2 separate steps to obtain a 4,000 fold dilution. Nonetheless, after commencement of intravenous vasopressin at 0.1 mU/kg/h with upward titration of the dose, there was a gradual but clear response over the next 72 h with normalization of both the serum sodium level to 140 mmol/L and the serum

Citation: Sng A, Loke KY, Lim Y. A Case of Neonatal Central Diabetes Insipidus in a Premature Infant – Challenges in Diagnosis and Management. Case Rep J. 2018;2(1):010

Time (hours)	Serum Sodium (mmol/L)	Serum Osmolality (mmol/kg)	Urine Osmolality (mmol/kg)	Vasopressin (mU/kg/hr)
0	152	313	69	0.1
6	154	313	78	0.5
15	144	300	119	1
24	147	307	65	1.5
36	150	310	141	2
48	148	305	133	2.5
60	144	300	131	3
66	133	269	291	3.4
72	140	280	285	3

Table 1: Biochemical response to intravenous vasopressin.

osmolality to 280 mmol/kg, with appropriately concentrated urine of 285 mmol/kg (Table 1).

The intravenous vasopressin was then converted to oral minirin (desmopressin acetate) and the dose was titrated to 3 micrograms per kg per dose 12 hourly, so as to maintain euvolemia with a urine output of 3 ml to 4 ml per kg per hour and a recommended total fluid intake of 160 ml per kg per day for homeostasis.

Assessment of his anterior pituitary profile (thyroid and hypothalamic pituitary adrenal axis) was normal.

Discussion

Neonatal CDI is rare as compared to NDI. In infants, CDI has been reported [2-8] with 1) meningitis caused by Group B *Streptococcus*, *Listeria* spp., toxoplasmosis and cytomegalovirus, 2) central nervous system malformations including holoprosencephaly and septo-optic dysplasia, 3) intraventricular hemorrhage, and 4) hypoxic ischemic encephalopathy.

We report a 25 week premature infant who sustained bilateral grade 3 ventricular intraventricular hemorrhages and subsequently developed hypernatremic dehydration. The paired sample of an elevated serum osmolality and inappropriately dilute urine confirmed the diagnosis of DI. In the neonatal age group, NDI (including the X-linked recessive forms) is more common [7] than CDI. Hence it was important to differentiate the two in our patient who was a premature baby with both central and renal insults.

The good response to treatment with synthetic intravenous vasopressin clinched the diagnosis of central DI. Other studies have used intranasal desmopressin as a diagnostic challenge [9] but none have reported using intravenous vasopressin. The advantage with the initial use of an intravenous vasopressin infusion lies in the controlled titration of the dose to establish response and in the clear differentiation of central from nephrogenic DI.

Central diabetes insipidus is traditionally treated with vasopressin or the use of desmopressin (a vasopressin analogue), which is more potent and has a five times longer half-life. Either a starting dose of 0.05 µg/kg/dose to 0.1 µg/kg/dose of intranasal vasopressin taken at an estimated 12 h apart or 0.5 µg/kg/dose to 1 µg/kg/dose of oral desmopressin ingested 12 h apart have been reported [10-12], with subsequent increasing titration of the dose to ensure clinical and biochemical response. Care must always be taken to prevent large fluctuations in serum sodium and osmolality. For this premature babe, the eventual desmopressin dose was 3 µg/kg/dose. This report adds to the world literature on the desmopressin dose which can be used in premature babies who develop CDI during infancy.

However, there are marked inter-individual differences in sensitivity to desmopressin which increases the difficulty in establishing the correct dose and frequency of administration for neonates. Moreover, the fixed anti-diuretic action of desmopressin and the high fluid intake necessary to meet caloric requirements of neonates with milk feeds increases the risk of hyponatremia [13]. If intravenous vasopressin is not available or if there are excessive fluctuations of sodium with vasopressin, hydrochlorothiazide coupled with a low renal solute feed has been reported to be a safe and efficacious alternative [14] in the treatment of central DI in neonates up to 6-12 months of age before transition to desmopressin.

Preterm neonates with previous intraventricular hemorrhage have been reported to have both transient and persistent CDI depending on the location of the damage in the hypothalamic-pituitary region. As such, an MRI of the brain is recommended if the CDI persists in infancy.

Conclusion

Although CDI is rare in the neonatal period, it is an important cause of hypernatremic dehydration, which should not be missed. In this patient, the only associated etiology was bilateral intraventricular hemorrhages. We have demonstrated that intravenous vasopressin infusion can be safely used to diagnose and treat CDI. The use of vasopressin in neonates is technically challenging with regard to both the 4,000 fold dilution and administration. However, if it is done accurately, intravenous vasopressin can allow for very close, controlled and safe titration of the dose balanced against the individual response, thus clearly differentiating CDI from NDI. To our knowledge, this is the first report in which intravenous vasopressin has been used to diagnose neonatal

CDI. Nonetheless, more experience is necessary to establish the use of intravenous vasopressin in the diagnosis and initial treatment of CDI.

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