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Coexistence of Central and Nephrogenic Diabetes Insipidus in a Preterm Infant

Michel-Macías Carolina[1], Cordero-González Guadalupe[2]

[1]Neonatology Fellow, Instituto Nacional de Perinatología, México; [2]Neonatal Intensive Care Unit, Instituto Nacional de Perinatología, México.

Corresponding Author:
Dr. Michel-Macías Carolina
Email: dra.carolinamichel@gmail.com

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Abstract

Background: Diabetes insipidus (DI) is a rare cause of hypernatremia in preterm newborns. Common causes of central DI include intra-ventricular hemorrhage, congenital infection and midline defects. Nephrogenic DI (NDI) is less frequent and can be caused by nephrocalcinosis. *Case Report*: We hereby report 665 gram female infant born at 27 weeks gestation with central DI and treated with desmopressin. The infant presented again with hypernatremia and showed a poor response to desmopressin. The finding of nephrocalcinosis oriented us to a nephrogenic component of DI. *Conclusion*: Although nephrogenic diabetes insipidus is the less frequent form of DI, preterm newborns present many risk factors for developing nephrocalcinosis (prolonged ventilation, diuretic therapy, dexamethasone, hypercalcemia) and NDI as a result. In a preterm newborn with CDI, a nephrogenic component must be suspected in the set of decreasing response to DDAVP.

Keywords: Diabetes Insipidus, Diuretics, Hypernatremia, Infant, Nephrocalcinosis.

Introduction

Endocrinal disorders are commonly associated with premature, low birth weight and small size for gestational age sick infants in neonatal intensive care unit (NICU) [1]. Diabetes insipidus (DI) is characterized by the inability to concentrate urine secondary to vasopressin deficiency or to vasopressin resistance resulting in polyuria and hypernatremia. Diagnosis of NDI is rarely made in very low birth weight (VLBW) and preterm infants since hypernatremic dehydration, high urine output, reduced ability to excrete sodium load and high transepidermal losses are common and manifestation of other infectious diseases commonly seen in neonates [2]. Diabetes insipidus is rare, with a prevalence estimated at 1:25,000. Central diabetes insipidus (CDI) accounts for greater than 90% of cases of DI. Nephrogenic diabetes insipidus (NDI) is less frequent and X-linked NDI accounts for 90% of cases [3].

In older children, the most common causes or CDI reported in case series are idiopathic CDI and intracranial tumors. However, CDI in infants is rare, and has been associated to intraventricular hemorrhage, congenital infection, midline defects and septo-optic dysplasia [4]. Non-heritable causes of nephrogenic DI include primary tubulointerstitial nephropathies (polycystic kidney disease, hydronephrosis, renal tubular acidosis, idiopathic hypercalciuria) and secondary tubule-interstitial nephropathies (hypercalcemia and nephrocalcinosis, kaliopenic nephropathy, medication induced) [5].

We report here a case of diabetes insipidus with both central and nephrogenic components in a VLBW newborn. To our knowledge, this is the first case of 'mixed' diabetes insipidus reported in a preterm newborn.

Case report

A 665 gram female infant was born by vaginal delivery at 27 weeks gestation to 24 year old mother. She received betamethasone and magnesium sulfate prior to delivery. The infant had Apgar scores of 3,6 and 8 at 1,5 and 10 minutes respectively. She developed severe respiratory distress syndrome and required surfactant administration and mechanical ventilation, hence she was transferred to the NICU. Trans-fontanelle-neurosonography on day two revealed a grade II intraventricular hemorrhage. On day 19 of life she underwent surgical duct ligation after two failed courses of ibuprofen. She developed hypernatremia on day 25 of life (164 mmol/L), which persisted despite increases in enteral feeds and free water replacement. On day 20 of life intravenous dexamethasone was administered to prevent extubation failure (0.78 mg/kg over 9 days). Urine output and serum sodium progressively increased to 6.1 ml/kg/hour and 168 mmol/L respectively on day 45 of life, which associated to serum osmolality of 376 mOsm/kg and urine osmolality of 255 mOsm/kg established the diagnosis of DI. She was started on intranasal desmopressin acetate (DDAVP) (0.2 µg/kg/dose) presenting an excessive response, with a decrease in sodium to 155 mmol/L and urine output to 1.9 ml/kg/hour. Because of these wide fluctuations, an oral formulation was started. DDAVP was repeatedly adjusted, reaching a 0.5 µg/kg/dose twice daily, with an adequate control in serum sodium levels. Subsequent trans-fontanelle-neurosonography on day 42 of life reported previous hemorrhage in reabsorption process and complete resolution on day 45. Evaluation of other pituitary hormone deficiencies revealed luteinizing hormone (LH): 64.8 mIU/mL, follicle-stimulating hormone (FSH): 57.3 mIU/mL, thyroid-stimulating hormone (TSH): 2.43 µIU/mL, free thyroxine (FT4): 1.05 ng/dL and cortisol: 1.47 µg/dL, for which hydrocortisone was started at a dose of 18 mg/m^2. Ophthalmologic evaluation revealed retinopathy of prematurity zone II stage I without findings suggestive of optic nerve hypoplasia. She underwent a magnetic resonance imaging scan of the brain on day 100 of life, showing no abnormalities on pituitary and hypothalamic views. By day 108 of life hypernatremia was again noted despite treatment with DDAVP, hence hydrochlorothiazide was prescribed (1 mg/kg/dose) and DDAVP dose progressively increased to 5 µg/kg twice daily due to persistent hypernatremia. A renal ultrasound revealed bilateral nephrocalcinosis. Reevaluation of urine osmolality revealed a one hour predose osmolality of 119.6 mOsm/kg and a postdose osmolality of 169.2 mOsm/kg, showing a poor response to DDAVP presumably due to a nephrogenic component complicating the clinical course of DI. Hydrochlorothiazide was continued at the same dose, reaching adequate serum sodium levels in the next 48 hours.

Discussion

In this report, although there was an evident response to DDVAP to establish the diagnosis of CDI, the etiology was not identified, hence it was determined to be 'idiopathic'. Despite the fact an intra-ventricular hemorrhage was observed on day 2 of life, its extension could not explain CDI. However, Karthikeyan *et al*. reported that three of five infants with idiopathic isolated congenital CDI were born very prematurely (gestational age < 30 weeks) and none of them had significant intracranial hemorrhage to explain CDI [6]. Chan *et al*. reported 2 cases of central diabetes insipidus in premature neonates with brain injury (periventricular leukomalacia, bilateral grade 2 intraventricular hemorrhage) and speculated that diabetes insipidus following intra-ventricular hemorrhage or ischaemic damage is not necessarily transient in nature and its duration depends on the location of damage in the pituitary glands [6]. Interestingly, Borenstein-Levin *et al*. reported the novel association between DI and hydrocephalus and the fact that such DI could be reversible with the reduction of ventricular size [7]. The presence of a hyper-intense signal of the posterior pituitary on a T1-weighted MRI scan reflects the functional

integrity of neurohypophysis, although absence is not pathognomonic of CDI and its presence does not discard DI [4].

The anatomical and pathophysiological basis of DI is relatively well understood. Damage or compromise of the hypothalamus above the median eminence may lead to permanent DI, whereas damage below this level, or disturbance of the posterior lobe of the pituitary gland, leads to transient DI because ADH can subsequently be released from nerve fibres ending in the median eminence. This explains why DI is transitory in some patients but not in others [8].

Nephrocalcinosis (NC) in preterm neonates occurs as a result of imbalance between stone-promoting and stone- inhibiting factors [9]. There is a clear correlation between prevalence of NC and low gestational age [9,10]. Premature kidneys have relatively well-developed deep nephrons, with a long loop of Henle and probably low urine velocity. As a result, conditions are favorable for the formation of crystals, which can stick to the surface and grow and aggregate in the tubules [9]. Moreover, an association between dexamethasone treatment, high calcium excretion and NC is found in preterm neonates [9,10]. Our patient received two courses of dexamethasone to prevent extubation failure. Apart from enhancing the development of nephrocalcinosis, dexamethasone could play a role in unmasking of diabetes insipidus, as has been well recognized. The effect of cortisol is due to a central suppression of the AVP response to an osmotic stimulus [11]. Initial evaluation of anterior pituitary hormone deficiencies in our patient revealed a low cortisol, hence hydrocortisone was started.

Also, our patient experienced periods of respiratory acidosis due to respiratory failure and bronchopulmonary dysplasia (71 days under mechanical ventilation, 3 days under HFOV). Acidosis results in a number of changes in adults that increase the risk of stone formation: increased urinary calcium as a result of bone buffering, decreased urinary citrate by increased reabsorption in the proximal tubule and decreased urinary pH [10]. Preterm neonates on mechanical ventilation had a low urinary citrate excretion when compared with a control group [10-12]. Once the response to DDAVP was noted to be poor, thiazide diuretics were administered with a starting dose of 1 mg/kg/day of hydrochlorothiazide. Nephrocalcinosis was suspected and then confirmed by sonography, revealing a nephrogenic component complicating CID.

The mechanism of the paradoxical antidiuretic effect of thiazide diuretics is not well understood. These drugs decrease the distal renal reabsorption of sodium, leading to increased sodium excretion, which causes extracellular volume contraction, leading to water and sodium reabsorption from the proximal tubule. This results in decreased water and sodium delivery to the distal tubule and the collecting duct, lowering urine output [13].

Conclusion

DI is a rare cause of hypernatremia which must be suspected in the NICU, as preterm newborns present many risk factors for both central and nephrogenic diabetes insipidus such as intraventricular hemorrhage, periventricular leukomalacia, nephocalcinosis and hypercalcemia. Although NDI is less frequent, an additional nephrogenic component should be suspected in the presence of a decreasing response to DDAVP. Reevaluation of pre and post-dose urine osmolality can support the addition of thiazides to the established treatment.

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