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Acid-Base and Electrolyte Teaching Case

Approach to the Treatment of the Infant With Hyponatremia

Jason H. Greenberg, MD, Alda Tufro, MD, PhD, and Olivera Marsenic, MD

Hyponatremia is an electrolyte abnormality that occurs in infancy due to a variety of inherited and acquired disorders. Infants with hyponatremia can present with neurologic symptoms such as vomiting, weakness, and seizures. Common causes of hyponatremia in the infant population are excess ingestion or administration of hypotonic fluids and excessive gastrointestinal salt loss. Hyponatremia in infancy also can be a sign of less common disorders, such as mineralocorticoid deficiency or resistance, and disregulation of arginine vasopressin with impaired free-water removal. Treatment of infants with hyponatremia is dependent on the severity of symptoms and the cause of hyponatremia. In nephrogenic syndrome of inappropriate antidiuresis (NSIAD), fluid retention is due to a gain-of-function mutation in the arginine vasopressin receptor 2 (AVPR2) gene leading to low arginine vasopressin levels. We describe the case of an infant with hyponatremia due to NSIAD, whose mother also has a known mutation in the AVPR2 gene. We report the approach to the treatment of hyponatremia and its unique challenges in infancy.

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INDEX WORDS: Hyponatremia; serum sodium concentration; vasopressin; arginine vasopressin receptor 2 (AVPR2); nephrogenic syndrome of inappropriate antidiuresis (NSIAD); urea; gain-of-function mutation; R137C; infancy.

INTRODUCTION

Hyponatremia (serum sodium concentration $<$ 135 mEq/L) occurs due to an inability to maintain a normal sodium and water balance. Sodium is the main determinant of serum osmolality, and changes in its serum concentration can result in fluid shifts between intracellular and extracellular compartments. Water influx into the intracellular space swells cells, which can cause cerebral edema and neurologic injury.

Infants with hyponatremia may present with neurologic symptoms such as vomiting, irritability, weakness, and seizures (Box 1).[1] In cases of maternal hyponatremia, fetal sodium rapidly equilibrates with maternal sodium, with fetal hyponatremia causing jaundice, tachypnea, and seizures in the fetus.[2] Most cases of hyponatremia in the infant population occur in hospitalized infants due to administration of hypotonic fluid, but also occur due to central nervous system pathology, pulmonary disease, or post-operative complications.[3-5] In the outpatient setting, hyponatremia in infants is less common, but can be caused by excess ingestion of free water and hypotonic fluids, such as overdiluted infant formula or plant milk, or by excess salt loss with diarrhea.[3,6,7] Hyponatremia is found in infants with less common disorders such as mineralocorticoid deficiency or resistance, hypopituitarism, inflammatory diseases, or dysregulation of arginine vasopressin (AVP).[8-11] We report the case of an infant with hyponatremia due to nephrogenic syndrome of inappropriate antidiuresis (NSIAD), with an approach to treatment of hyponatremia and its unique challenges in infancy.

CASE REPORT

Clinical History and Initial Laboratory Data

An asymptomatic 7-month-old male infant presented with serum sodium concentration of 123 mEq/L. The test was ordered by the pediatrician because of a maternal history of hyponatremia due to an X-linked AVP receptor 2 (AVPR2) gain-of-function mutation. An accompanying teaching case describes the case of the infant's mother.[12] The infant was born full term, had normal growth and development, and was exclusively breast-fed. He appeared well and euvolemic. Weight was 8.02 kg (21st percentile for age), length was 72.0 cm (77th percentile for age), and blood pressure was 97/71 mm Hg. Initial laboratory testing demonstrated serum sodium concentration of 119 mEq/L, serum osmolality of 251 mOsm/kg, urine osmolality of 109 mOsm/kg, and urine sodium concentration $<$ 10 mEq/L. Serum creatinine level was 0.2 mg/dL, with estimated glomerular filtration rate of 149 mL/min/1.73 m^2 as calculated by the Schwartz formula.[13] Kidney ultrasound findings were normal. Oral sodium chloride supplementation was started.[14] To ensure higher solute intake, breast-feeding was partially replaced with infant formula, and introduction of baby foods was encouraged.

Additional Investigations

Hyponatremia persisted, with a serum sodium concentration range of 114 to 122 mEq/L and increased thirst while on sodium

From the Division of Pediatric Nephrology, Yale University School of Medicine, New Haven, CT.

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Address correspondence to Olivera Marsenic Couloures, MD, Yale University School of Medicine, Division of Pediatric Nephrology, 333 Cedar St, New Haven, CT 06510. E-mail: olivera.couloures@yale.edu

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Box 1. Symptoms of Hyponatremia in Infants and Children

- Nausea
- Vomiting
- Headache
- Weakness
- Confusion
- Behavioral changes
- Impaired response to verbal and tactile stimuli
- Seizures

Data from.[1,3,17]

chloride supplementation, which then was discontinued. Treatment with urea powder administered in a 30% solution was started. The initial dose was 0.1 g/kg/d divided into 4 doses, with the plan to increase the dose to 2 g/kg/d.[15] Monitoring included laboratory testing (serum sodium, serum urea nitrogen, serum osmolality, urine sodium, and urine osmolality) and assessments of volume status and changes in weight (Table 1). Management was continued with the goal to increase solute load (fortifying the breast milk with a 24-kcal fortifier and increasing urea powder dose) and decrease free-water intake (fluid restriction to 80% of maintenance needs). Antidiuretic hormone (ADH) levels were undetectable. Genetic testing (performed by Athena Diagnostics) confirmed a hemizygous mutation in the AVPR2 gene, a cytosine to thymine substitution at nucleotide 770 of the complementary DNA, predicted to lead to a substitution of arginine to cysteine at amino acid 137. This mutation previously has been found to be activating and inherited in an X-linked dominant fashion.[11] The identical mutation was identified in the mother and was not detected in the sole female sibling.

Diagnosis

NSIAD due to an X-linked AVPR2 gain-of-function mutation.

Clinical Follow-up

Serum sodium concentrations improved and remained at 126 to 137 mEq/L (Table 1). There was difficulty administering the prescribed urea dose, which was improved by adding the sweetener stevia, a sugar substitute made from plant leaves. Advancing the infant's diet to baby foods and solids was very slow. Developmental assessment revealed mild gross motor delay. The infant was last seen at 17 months of age when his weight was 10.9 kg (26th percentile for age), height was 82 cm (53rd percentile for age), and serum sodium concentration was 137 mEq/L on a urea dosage of 1.7 g/kg/d. Serum creatinine level remained at 0.2 mg/dL, with estimated glomerular filtration rate of 149 mL/min/1.73 m^2. Gross motor delay was substantially improved. As his intake of baby foods and solids improved, fortification of breast milk was stopped. He remains on a fluid restriction of 80% of maintenance needs.

DISCUSSION

Hyponatremia in infants and children can be caused by a variety of medical problems (Box 2), with free-water excess being more common than sodium depletion.[16-18] The cause of hyponatremia can be distinguished by performing a careful history, assessing the patient's volume status, and measuring plasma osmolality, urine osmolality, and urine sodium (Box 3).[16] In volume-depleted states, low urine sodium concentration results from urine sodium reabsorption, whereas high urine sodium concentration indicates tubulopathy, cerebral salt wasting, adrenal insufficiency, or diuretic use.[18] In euvolemic or hypervolemic states, high urine sodium concentration and high urine osmolality are suggestive of the syndrome of inappropriate ADH secretion (SIADH), characterized by impaired free-water excretion.[16,19]

Serum sodium concentration is affected by renal water reabsorption, which is controlled primarily by AVP. The hypothalamus produces AVP, which, when triggered by osmotic and hemodynamic stimuli, is released from the posterior pituitary. AVP promotes water reabsorption by increasing the water permeability of the collecting tubule of the kidney.[1] Abnormalities in AVP secretion or AVP receptor function result in abnormal free-water excretion. In utero, maternal hyponatremia suppresses fetal ADH production, resulting in increased fetal urine output and polyhydramnios.[2] SIADH and NSIAD have the same clinical features of impaired free-water excretion (hyponatremia, serum hypo-osmolality, and inappropriately concentrated urine) but differ by ADH level, which is high in SIADH and undetectable in NSIAD (Box 3).[11,20] A previously reported X-linked vasopressin receptor gain-of-function mutation causing NSIAD was confirmed in our patient.[11,15] AVPR2 is 1 of 3 AVP receptors, localized to the

Table 1. Serial Laboratory Data

Age (mo)	Weight (kg)	Urea Dose (g/kg/d)	Serum Sodium (mEq/L)	Serum Osmolality (mOsm/kg)	SUN (mg/dL)	Urine Osmolality (mOsm/kg)	Urine Sodium (mEq/L)
7	8.02	—	119	251	3	109	<10
8	8.40	0.1	118	—	7	128	27
8.5	8.44	1.75	130	281	31	—	—
9	8.58	2	132	282	26	—	—
10	9.17	2	126	273	28	665	<10
12	9.62	2	129	285	47	788	75
13	9.70	2	135	301	54	960	17
17	10.90	1.7	137	304	44	1,000	27

Note: Conversion factor for SUN in mg/dL to mmol/L, ×0.357.
Abbreviation: SUN, serum urea nitrogen.