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BRIEF REPORT

Hyponatremia resulting from Arginine Vasopressin Receptor 2 gene mutation

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Abstract Chronic hyponatremia, unless associated with extracellular fluid volume expansion, is an infrequent electrolyte imbalance in pediatrics. We report an infant with chronic hyponatremia suggestive of a syndrome of inappropriate secretion of antidiuretic hormone (SIADH), in the absence of ADH secretion. A mutation was found in the same codon of the gene that results in a loss-of-function of arginine vasopressin receptor 2 (AVPR2) observed in congenital nephrogenic diabetes insipidus. In this case, a gain-of- function of AVPR 2 was found to be responsible for a SIADH-like state.

Keywords Seizure · Syndrome of inappropriate secretion of antidiuretic hormone · AVPR2 · Water excretion · Nephrogenic syndrome of inappropriate antidiuresis · Hypo-osmolarity syndrome of inappropriate antidiuresis

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Introduction

Hyponatremia is defined by some authors as a decrease in serum sodium concentration below 136 mEq/l [1, 2], others define it when it is 130 mEq/l or less [3, 4]. Hypotonic hyponatremia represents an excess of water in relation to sodium stores [1]. These may be decreased, increased or essentially normal. Hyponatremia may be further associated with an extracellular fluid volume that is contracted, increased or also essentially normal [1, 2]. In hyponatremia associated with contracted fluid volume, hemodynamic compromise occurs and is what usually determines the patient's clinical manifestations. However in hyponatremia associated with normal or increased extracellular volume, neurological symptoms such as seizures are presenting signs that warrant hospital admission [2, 4]. The purpose of this presentation is to describe the diagnosis and outcome of an infant who presented chronic hyponatremia with normal extracellular fluid volume.

Case report

A five-and-a-half-month-old infant was admitted to the Hospital Nacional de Pediatría "Prof. Dr. Juan P. Garrahan" in Buenos Aires, Argentina for hyponatremia. A week earlier, he had been admitted to another hospital for a 20-minute seizure associated with a serum sodium concentration of 112 mEq/l. The value was corrected intravenously but the cause of hyponatremia was not established. He was discharged with serum sodium values of 139 mEq/l. Two days later his serum values were 120 mEq/l, and he was referred to the Hospital "Garrahan".

On admission, the child was an apparently healthy infant whose physical exam was unremarkable. His past medical history revealed that he was the 3rd child of non-consanguineous parents. He was an exclusively breast-fed infant with a history of mild wheezing episodes. His growth and development had been adequate. His mother was not taking any medications. He appeared to be euvolemic. His weight was 8.4 kg (Percentile 75). His blood pressure was 90/50 mmHg (Percentile 50). An initial laboratory workup showed the following results: blood [Na^+]: 124 mEq/l, [K^+]: 4 mEq/l, [CL^-]: 98 mEq/l, urea: 18 mg/dl, venous blood gases: pH: 7.39, pCO_2: 38 mmHg, pO_2: 66 mmHg, bicarbonate: 22.5 mmol/l, base excess: −1.6, albumin: 3.3 g/dl, urinary sodium: less than 10 mEq/l, urinary potassium: 5 mEq/l. Increased and decreased extracellular volume associated hyponatremic states were ruled out on the basis of his history, physical examination and laboratory studies. Other laboratory values of the patient are described in Table 1. As urine osmolality was higher than expected for the serum osmolality, a presumptive diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was made [5]. However, the child was not suffering any of the acute or chronic diseases that Zerbe, Stropes and Robertson describe as causing this syndrome [6]. In order to maintain serum sodium levels above 130 mEq/l, he required between 4 and 6 mEq/kg/day of oral sodium chloride. He did not have marked variations in weight.

Table 1 Laboratory values of the patient

Laboratory studies		Reference values [16]
a) Serum and plasma		
Sodium (mEq/l)	124	139–146
Potassium (mEq/l)	4	3.5–6
Chloride (mEq/l)	98	98–106
Bicarbonate (mmol/L)	22	22–29
Creatinine (mg/dl)	0.1	0.2–0.4
Urea (mg/dl)	18	5–18
Albumin (g/dl)	3.3	3.9–5
Osmolality (mOsm/kg H_2O)	261	275–295
Thyrotropin (mIU/L)	1.79	0.7–6.4
Triiodothyronine (ng/dl)	208	100–260
Thyroxine (ug/dl)	12.3	6.2–22
ACTH (Adrenocorticotropic hormone) (pg/ml)	29.9	25–100
Cortisol (ug/dl)	13.8	5–23
AVP (Arginine vasopressin) (pg/ml)	<1	<1.5–12[a]
b) Urine		
Osmolality (mOsm/kg H_2O)	468	50–1400[b]
Sodium (mEq/l)	25	40–220[c]
Potassium (mEq/l)	83	2.5–125[c]
c) Sweat Test (mmol/L)	23	<40

[a] Serum osmolality dependent, [b] Fluid intake dependent, [c] Diet dependent

To further explore his disorder, sodium chloride was discontinued for 2 days and plasma and spot urine samples were obtained for simultaneous sodium concentration, AVP (Arginine Vasopressin) levels and osmolality studies. The following values were obtained after the 2-day sodium withdrawal: Plasma AVP: <1.0 pg/ml; serum osmolality: 261 mOsm/kg H_2O; serum [Na^+]: 127 mEq/l; serum [K^+]: 5.6 mEq/l; Urine AVP: 15 pg/ml; urine osmolality: 438 mOsm/kg H_2O; urine [Na^+]: 25 mEq/l, urine [K^+]: 83 mEq/l. The results show a higher urine osmolality than expected for the plasma osmolality, with undetectable AVP plasma levels. They are consistent with a type 4 or D pattern of SIADH as described by Zerbe, Stropes and Robertson [6]. Oral sodium chloride was reintroduced 24 hours later when serum sodium values of 120 mEq/l were reached.

With the diagnosis of SIADH and as he was 7 months old and with an adequate neurological development, solid food was introduced with the purpose of weaning him to reduce liquid intake. After 3 weeks he was eating more, breast feeding less, and requiring less sodium. A month after beginning to eat solid foods, all oral sodium chloride was suspended and his serum sodium concentration stabilized in the 140 mEq/l range with high urine Na^+ excretion. Although water intake was not restricted, it was recommended that it be supervised so as to avoid abrupt serum osmolality changes.

When he was 20 months old, he suffered another seizure. It had been a very hot day and he had drunk more water than usual. His laboratory values were serum [Na^+]: 125 mEq/l, serum osmolality 260 mOsm/kg H_2O and urine osmolality 405 mOsm/kg H_2O. EEG was normal. He recovered without neurological sequelae.

When he was 5 years of age, a water loading test (20 ml/kg) was performed for further evaluation. His serum osmolality decreased from 275 mOsm/L to 270 mOsm/L, increasing thereafter again to 275 mOsm/l. The urine osmolality initially was 1000 mOsm/kg H_2O, and never decreased below 650 mOsm/kg H_2O. Three hours after he drank the water, the serum and spot urine osmolarity were 275 mOsm/kg H_2O and 780 mOsm/kg H_2O, respectively.

DNA sequencing for arginine vasopressin receptor 2 gene (AVPR2) was performed. The study is positive for a mutation in the *AVPR2* gene. The mutation detected is R137C, where the cytosine in nucleotide 770 is mutated to thymine. This changes the normal amino acid arginine at codon 137 to cysteine, (Fig. 1). The genetic data are consistent with the diagnosis of nephrogenic syndrome of inappropriate antidiuresis (NSIAD) as described by Feldman et al. in 2 infants [7]. In their article, Feldman

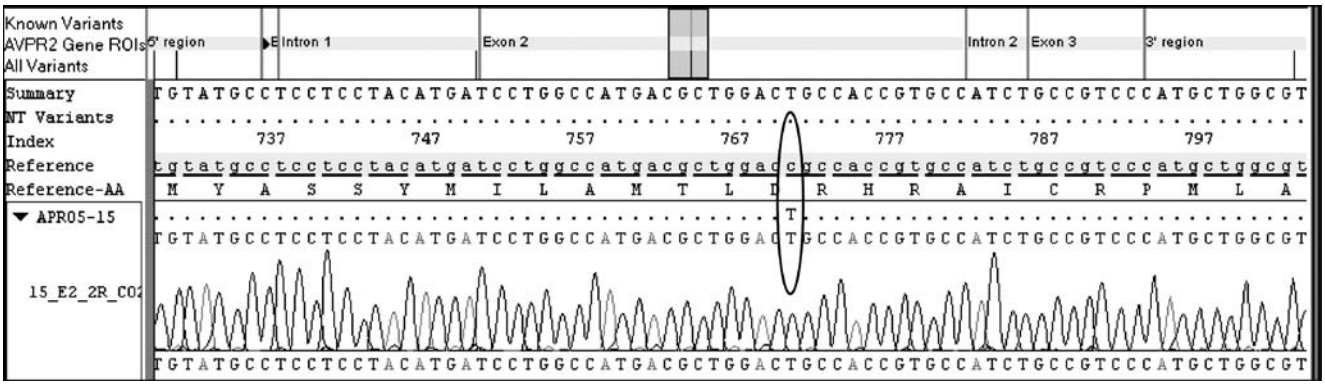

Fig. 1 Patient's *AVPR2* gene DNA sequencing showing mutation R137C, g770C>T

et al. also report how they developed a functional assay for *AVPR2* gene and how their results show that R137C mutations are active mutations [7]. Genetic studies were then performed on his mother and siblings. She was found to be a heterozygous carrier of the mutation previously detected in her son. His siblings (2 brothers and a sister) do not carry the mutation.

The child has grown well. He is currently 11 years old. His weight is 47.5 kg. (Percentile 50–75) and height 1.53 M (Percentile 90–97). His blood pressure is 115/60 mmHg (Percentile 75–90). His last laboratory results performed when he was 10 years old were, serum [Na^+]: 136 mEq/l, [K^+]: 4.2 mEq/l, osmolality: 287 mOsm/kg H_2O; spot urine [Na^+]: 166 mEq/l, [K^+]: 210 mEq/l, osmolality: 1467 mOsm/kg H_2O. His school performance is average and he also participates in extracurricular activities. He self regulates the liquid intake now. He drinks about a liter of water per day. His salt intake has not been quantified; however, his mother regards it as normal. On hot days or after sports, he drinks sports drinks that contain electrolytes. The sodium concentration of these drinks is equivalent to the concentration of sodium he loses in perspiration. If he does drink more than usual, or more abruptly as in social gatherings or on hot summer days, he eats a salty snack.

Discussion

Chronic hyponatremia, unless associated with extracellular volume expansion, is an uncommon electrolyte imbalance in the pediatric setting. Therefore, chronic hyponatremia with essentially normal extracellular fluid volume warrants studies related to water and salt metabolism.

This patient presents an unusual cause in the disturbance of water homeostasis. He presents almost all the findings of SIADH as described by Bartter and Schwartz [5]: a) hyponatremia with corresponding hypo-osmolality of the serum and extracellular fluid, b) higher urine osmolality than expected for concomitant plasma osmolality, c) absence of clinical evidence of fluid depletion, d) normal renal function and e) normal adrenal function. Absence of edema forming states has been added to the definition. Continued renal sodium excretion is another finding of SIADH according to Bartter and Schwartz [5]. Initially, the patient did not manifest this feature. This took place when his serum sodium concentration approached 120 mEq/l. Continued urinary sodium excretion ensued when oral sodium chloride was administered and the serum sodium concentrations reached or surpassed 130 mEq/l. This may be explained by the fact that at very low serum sodium concentrations, sodium excretion reflects sodium intake and breast milk has very low sodium content.

The child's serum sodium concentration, vasopressin dosage and osmolality and urine osmolality corresponded to what Zerbe, Stropes and Robertson classified as type D or 4th pattern of SIADH [6]. These patients exhibit what they termed "hypovasopressinemic antidiuresis". The authors hypothesize that this could be due to either an increased sensitivity to ADH or to another antidiuretic substance immunologically distinct from ADH [6]. Feldman et al. have proposed the term syndrome of inappropriate antidiuresis (SIAD) for this group of patients [7]. Tanaka et al. have reported a SIADH-like condition in the absence of inappropriate ADH secretion, in females from a third-generation Japanese family that has normal *AVPR2* gene studies [8]. In this patient, however, DNA sequencing for the *AVPR2* gene was positive for a mutation in the *AVPR2* gene. The detection of this mutation is consistent with the diagnosis of the newly described nephrogenic syndrome of inappropriate antidiuresis (NSIAD) as described by Feldman et al. [7]. Due to this mutation, the AVPR2 is persistently activated, manifesting an inability to excrete a free water load [7]. This gain-of-function mutation exhibits an inappropriate concentrated urine, hyponatremia and serum hypo-osmolality [7]. An interesting observation is that a single mutation at the same codon may result in either a loss-of-function or a gain-of-

function of the same receptor [7]. That is congenital nephrogenic diabetes insipidus or NSIAD [7].

Water restriction is the treatment for SIADH [9]. This is practicable for acute and short term SIADH such as that seen in certain disorders of the nervous system and certain pulmonary infections. In chronic conditions, this is difficult to achieve and different drugs have been proposed as treatment options [9]. Lithium [10], demeclocycline [11] and phenytoin [12] have been used, but in certain cases with adverse effects. Recently, Huang et al. treated 2 pediatric patients with oral urea with good results and no toxic effects [13]. Breast milk is the natural food for full-term infants during the first months of life [14, 15]. Infant daily liquid intake is in the 120–150 ml/kg range during the 1st year of life. This high liquid intake needed to meet nutritional requirements can lead to neurological complications in infants with SIAD. Feldman et al. successfully used oral urea as treatment in their infant patients [7].

We initially treated this patient, while he was breast feeding, with oral sodium chloride because serum sodium concentrations decreased to levels that could induce seizures when sodium chloride was withheld. Although his serum sodium concentrations improved, normal serum sodium levels were not attained. The osmolalities we observed in our patient with NSIAD varied. We speculate that the effects on water homeostasis of the up regulated AVPR2 in patients with NSIAD, may not be the same as those of AVPR2 of patients with SIADH that do have high plasma AVP concentrations. This could explain why he improved with oral sodium chloride supplementation and also why now with his current liquid intake, marked hyponatremia is not observed. Functional studies of the AVPR2 in the setting of NSIAD and SIADH at different AVP serum levels would be required to further explain this situation.

In order to decrease his very high liquid intake and as he was adequately developed neurologically at the age of 7 months, we introduced solid food. Adequate growth has been achieved and, except for a seizure when he was 20 months, he has suffered no further complications. Currently, he self-regulates his intake. This probably has to do with his upbringing regarding liquid intake. He is aware that his kidneys cannot handle an abrupt liquid intake; therefore he knows that it must be spread out over time.

This case report's long term follow-up raises the possibility that pharmacological treatment can be withdrawn early in life, provided a supervised liquid intake approach is applied; specially in early childhood. As the child grows older, self-regulated liquid intake may be accomplished. On special occasions, sport drinks that contain electrolytes or salty snacks may be warranted to avoid abrupt serum osmolar changes.

Up regulation of AVPR2 is a novel etiology for SIAD. In Tanaka et al.'s paper the disease was reported in female family members. In Feldman et al.'s article and in this report, females are carriers and male members can exhibit the disease. Further studies are necessary to elucidate the various mechanisms of SIAD and their genetic mode of transmission.

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