Case Report

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Urea as safe treatment for hyponatremia due to syndrome of inappropriate antidiuretic hormone in infant with solitary central incisor and neurofibromatosis-1

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Abstract

Objectives: Classic treatment for syndrome of inappropriate antidiuretic hormone (SIADH) is fluid restriction. However, this is not ideal for infants who need large fluid volumes to ensure adequate caloric intake for growth. The use of urea has not been thoroughly studied in children.
Case presentation: This infant had SIADH complicated by poor growth, solitary central incisor, and NF1. Following failed attempts to correct hyponatremia with fluid restriction and other therapeutics, urea normalized sodium levels and allowed liberalization of formula volumes, which resulted in improved weight gain.
Conclusions: Urea is a safe, cost-effective, long-term treatment for SIADH in infants who are unable to fluid restrict due to caloric goals.

Keywords: SIADH; solitary central incisor; urea.

Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is characterized by unregulated release of arginine vasopressin (AVP), which acts on V2 receptors (V2R) to increase renal expression of aquaporin-2 channels for water reabsorption [1]. SIADH can be idiopathic or arise due to medications, such as antipsychotics and anticonvulsants, or ectopic production of AVP by cancers, as well as following brain surgery, head trauma, or infections such as pneumonia. It is generally considered a diagnosis of exclusion and manifests as euvolemic hyponatremia with oliguria. Elevated levels of plasma AVP may also be seen in SIADH, a finding that is absent in nephrogenic SIADH, a condition involving an activating mutation in the gene for V2R. Regardless of etiology, patients with severe hyponatremia are at risk of seizures and brain herniation.

Fluid restriction is the primary treatment of SIADH. In contrast to recommended chronic hyponatremia management in adults, which includes options such as oral sodium chloride (NaCl), hypertonic saline, loop diuretics, V2R antagonists (vaptans), and urea, pharmacologic options for children are less established [1]. We present a case of an infant with SIADH, a solitary central incisor whose chronic hyponatremia was corrected with urea, and neurofibromatosis-1 (NF1).

Case presentation

First admission

A 12-day old infant born at 34 weeks of gestation was transferred to a level IV NICU for suspected congenital choanal stenosis and persistent hyponatremia. At the outside hospital, baseline labs showed low serum sodium of 126 mmol/L and serum osmolality of 260 mOsm/kg with urine output of 0.9 mL/kg/h. Total fluid volume was 80 mL/kg/day initially but then decreased to 60 mL/kg/day. Subsequently, sodium rose to 135 mmol/L and urine output improved. After feeds were increased, sodium plummeted to 128 mmol/L. At that time, FeNa was 0.7% and urine output was 2.2 mL/kg/day. Rather than reducing formula intake, 2 mEq/kg/day of NaCl supplementation

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was started. Laboratory data and clinical markers are summarized in Table 1.

Meanwhile, further evaluation revealed that the infant had pyriform aperture stenosis. Nasal prednisolone drops were initiated. To exclude additional endocrinopathies, imaging and laboratory analysis were pursued. MRI unveiled a midline defect of a solitary central incisor [Figure 1] and a normal pituitary gland. Renal ultrasound showed normal kidneys for age. Endocrinological work up (Table 2) included ACTH stimulation testing that returned normal, thus ruling out adrenal insufficiency or suppression secondary to prednisolone use. Laboratory analysis ruled out thyroid and aldosterone abnormalities. Genetic microarray testing returned negative. At 28 days of age, with serum sodium of 135 mmol/L, the patient was discharged on 6 mEq/kg/day of NaCl and 150 mL/kg/day of 22 kcal/oz fortified formula.

Second admission

Within a month, the patient was readmitted for acute respiratory distress secondary to coronavirus NL63 infection. During this admission, café au lait macules were noted and a diagnosis of NF1 was made after genetic evaluation. Her hospital stay was complicated by suboptimal weight gain and poor oral intake that led to placement of a nasogastric tube. A diagnosis of SIADH was suggested by serum sodium of 129 mmol/L and serum osmolality of 278 mOsm/kg at a time when urine sodium was 62 mmol/L, FeNa was 0.1%, and urine osmolality was 618 mOsm/kg. NaCl supplementation was increased to 8 mEq/kg/day and fluid intake restricted to 130 mL/kg/day. She had a vasopressin level measured during an episode of hyponatremia, which was elevated to 13.2 pg/mL while sodium was 125 mmol/L.

Since it was not ideal to further fluid restrict, fludrocortisone 0.1 mg was initiated. It was discontinued after two days as serum sodium remained stagnant and blood pressures increased. Furosemide 1 mg/kg/day was trialed but was discontinued due to minimal change in urine output and conclusion that it would not be an effective long-term solution. At 72 days of age, the infant was started on 0.5 g/kg of urea dissolved in 5 mL of formula, then divided in three doses per day. Salt supplementation at 10 mEq/kg/day was continued. Urea dosage was titrated up to 1.92 g/kg/day incrementally over a couple weeks as serum sodium began to trend upwards. Fluid restriction was discontinued, and feeds were maximized to promote weight gain. See Table 1 for laboratory and clinical measures in response to the above treatments.

The patient experienced intermittent emesis after initiation of urea, but overall, tolerated it well when spaced out from her formula tube feeds. Emesis then resolved with a formula change. At discharge, her serum sodium was 134 mmol/L on 1.9 g/kg/day of urea and 5 mEq/kg/day of NaCl supplementation.

Outpatient

The patient maintained stable serum sodium levels (130–145 mmol/L) while on 2 g/kg/day of urea. She had no fluid restriction and demonstrated appropriate weight gain. Over time, NaCl supplementation was discontinued, and urea was titrated down. By 20 months of age, urea was stopped completely. To date, at three years of life, the patient is no longer hyponatremic as sodium levels remain 140–144 mmol/L off treatment.

Discussion

Fluid restriction is the standard of care for hyponatremic patients due to SIADH [1]. We present an infant with a midline defect of a solitary central incisor and NF1 admitted for chronic hyponatremia secondary to SIADH. Although a midline defect of the central incisor has been associated with pituitary hypoplasia [2], MRI revealed our patient had a structurally normal pituitary gland. Genetic and laboratory analysis and imaging excluded many endocrinopathies and renal disease, which corroborated a diagnosis of SIADH. Since the patient's admission was complicated by poor weight gain, she was not an ideal candidate for fluid, and thus caloric, restriction. The patient's hyponatremia was refractory to NaCl supplementation alone, fludrocortisone, and furosemide, and was ultimately corrected with urea combined with NaCl supplementation.

Urea is an osmotic agent that normalizes serum sodium levels through diuresis and by reducing natriuresis [3]. It does not negatively impact other electrolyte levels and does not carry significant contraindications or drug interactions. Multiple publications have demonstrated the efficacy of urea [4, 5]. Four cases of its use in children with doses ranging from 0.1 to 2 g/kg/day are described with successful normalization of sodium levels along with eliminating the need for fluid restriction [4]. It is commercially available as a medical food product called ure-Na (Phoenix, Arizona, United States) in a lemon lime flavored powder [6]. A packet of ure-Na contains 15 g of urea that can be diluted in water into smaller dosages and stored covered

Table 1: Laboratory data and clinical markers of an infant admitted for persistent hyponatremia across two admissions.

	First admit	Fluid restriction	Increased fluids, initiated NaCl	First discharge	Second admit	Fludrocortisone stopped after 2 Days of treatment	Lasix stopped after 2 days of treatment	On 0.5 g/kg/day of urea	On 1.27 g/kg/day of urea	On 1.64 g/kg/day of urea	On 1.92 g/kg/day of urea, day prior to discharge	Reference range
Serum studies												
Na, mmol/L	126	135	128	135	129	128	135	125	132	134	134	132–142
Osmolality, mOsm/kg	260	–	263	280	278	–	–	270	–	296	–	275–296
AVP, pg/mL	–	–	–	–	–	–	–	13.2	–	–	–	0.0–6.9
Urine studies												
Na, mmol/L	–	–	24	81	62	–	–	90	–	–	–	NA
Output, mL/kg/h	0.9	2–3	2.2	3.73	3.51	3.32	2.14	1.26	4.28	3.72	3.06	NA
Osmolality, mOsm/kg	–	–	–	252	618	–	–	552	–	–	–	50–645
FeNa, %	–	–	0.7	1.8	0.1	–	–	0.7	–	–	–	NA
Other clinical markers												
Total fluid volume, ml/kg/day	80	60	150	150	130	120	140	140	150	150	150	NA
NaCl supplement, meq/kg/day	NA	NA	2	6	5.5	7	10	6[a]	10	10	10	NA
Weight, kg	2.17	2.13	2.27	2.44	2.93	3.01	3.1	3.30	3.36	3.40	3.53	NA

NA, not applicable; [a]NaCl supplement was temporarily decreased due to rapid increase in urine Na following initiation of urea. Urine Na then decreased and NaCl supplement was subsequently increased.

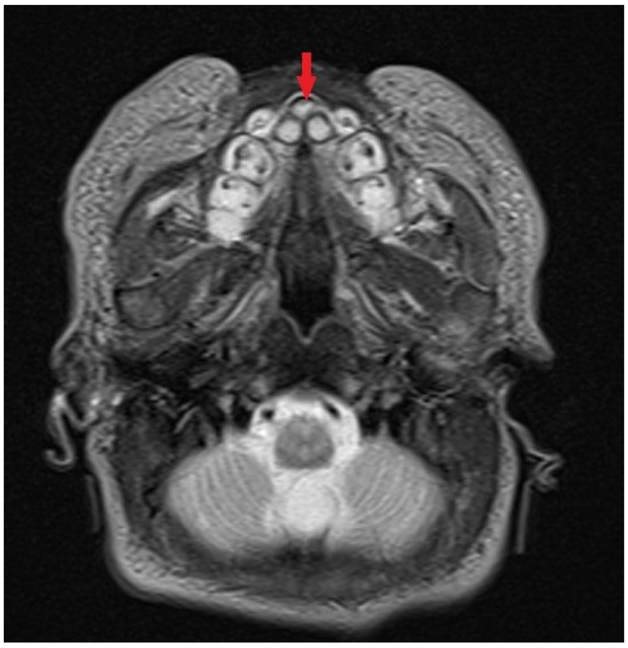

Figure 1: Brian MRI showing solitary central incisor.

Table 2: Endocrinological evaluation of an infant diagnosed with SIADH, single central incisor, and NF1.

	Patient value	Reference range
Serum studies		
TSH, mcIU/mL	3.6	0.35–7.6
Free T4, ng/dL	1.8	0.8–1.9
Renin activity, ng/mL/h	<0.65	1.4–7.8
Aldosterone, ng/dL	15	6.5–86
ACTH stimulation		
Cortisol, 0 min mcg/dL	6.9	≥1.1
Cortisol, 60 min, mcg/dL	32.2	>18

in the refrigerator for up to three days. Its main adverse reaction is mild gastrointestinal distress. Our patient's insurance covered the cost of ure-Na, but even without coverage, it is reasonably priced (8 packets for $29.90) [6]. Additionally, laboratory grade urea mixed with orange juice has been successfully used in adults and is cost effective [7]. This may be an effective option in pediatrics when precise and smaller dose adjustments may be needed.

Vaptans, which block aquaporin-2 channels, lead to an increase in water excretion, have demonstrated similar efficacy as urea in chronically hyponatremic adults [1]. Their use is still being explored in children [8, 9]. One case report presented correction of sodium after administering tolvaptan crushed in fortified formula to a premature infant with SIADH secondary to a hypothalamic abnormality [8]. However, vaptans carry a Food and Drug Administration black box warning for hepatotoxicity. Vaptans are also metabolized by hepatic CYP3A enzymes, thus cannot be used concomitantly with CYP3A inhibitors, including certain antibiotics and antifungals. As a result, vaptans require intensive monitoring of liver function, should only be initiated in the inpatient setting, and may not be tolerated for chronic use [8, 9]. Moreover, this class of drugs is expensive. The starting dose of tolvaptan (15 mg) is over $450, whereas conivaptan (20 mg/100 mL) is close to $1,000, making it cost-ineffective when there are cheaper therapeutics [10].

Furosemide, a loop diuretic, also enhances free water excretion and has been used with NaCl supplementation for pediatric hyponatremia [1, 11]. However, the drug when used alone can worsen hyponatremia as it promotes urinary loss of sodium. Additionally, outside of its typical use in adrenal insufficiency, fludrocortisone can be used to increase renal reabsorption of sodium leading to correction of hyponatremia [9, 12]. Other plausible pharmacologic options are demeclocycline and lithium which induce nephrogenic diabetes insipidus [1, 9]. There are no published studies of their use in treating pediatric hyponatremia, and in general, they are not recommended because of their substantial risk for toxicity.

It is unclear whether patients with NF1 are at an increased risk for SIADH and what underlying mechanisms may play a role. However, studies show that neurofibromin regulates hypothalamic function and pituitary development in the central nervous system by modulating intracellular cAMP levels. Loss of neurofibromin leads to pituitary dysfunction which is most often seen by a smaller anterior pituitary gland and hyposecretion of anterior pituitary hormones. Size of posterior pituitary has shown to be preserved. However, it is possible there are other effects of neurofibromin and the loss of it in individuals with NF1 that could affect vasopressin secretion from the pituitary gland [13].

In summary, urea is a safe therapeutic that can correct chronic hyponatremia due to SIADH in children as young as 2 months old. Unlike other agents, urea does not carry significant adverse effects and is more cost-effective. Moreover, urea can be safely utilized in the outpatient setting while electrolytes are followed. This makes it an attractive option within pediatrics as fluid restriction is not always a reasonable approach. Clinical studies with larger groups of pediatric patients and additional follow-up will broaden our understanding of urea use for chronic hyponatremia due to SIADH.

Learning points

- SIADH can be a complication in infants with a solitary central incisor and NF1.
- Urea is a safe alternative to fluid restriction in treating hyponatremia in pediatric patients and can be used long term. In contrast to vaptans, urea is more cost-effective and carries a greater safety profile.

What is new?

- The youngest (2-month old) child among published reports whose hyponatremia was corrected with urea.
- First reported case of SIADH in an infant with a solitary central incisor and neurofibromatosis-1 (NF1).

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