Adipsic Diabetes Insipidus in Children: A Case Report and Practical Guide

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Patient: Male, 2-year-old
Final Diagnosis: Adipsic diabetes insipidus
Symptoms: Dehydration • polyuria
Medication: Desmopressin
Clinical Procedure: Fluid replacement
Specialty: Pediatrics and Neonatology • Endocrine and Metabolic

Objective: Rare coexistence of disease or pathology
Background: Diabetes insipidus (DI) is a clinical syndrome characterized by polyuria and polydipsia that result from a deficiency of antidiuretic hormone (ADH), central DI, or resistance to ADH, nephrogenic DI. In otherwise healthy patients with DI, normal thirst mechanism, and free access to water, the thirst system can maintain plasma osmolality in the near-normal range. However, in cases where DI presents with adipsia, cognitive impairment, or restricted access to water, true hypernatremia may occur, leading to severe morbidity and mortality.

Case Report: We report a case of a 2-year-old boy who had global developmental delay and post-brain debulking surgery involving the hypothalamic region, which resulted in central DI and thirst center dysfunction. We describe the clinical presentation, the current understanding of adipsic DI, and a new practical approach for management. The main guidelines of treatment include (1) fixed desmopressin dosing that allows minimal urinary breakthroughs in-between the doses; (2) timely diaper weight-based replacement of water; (3) bodyweight-based fluid correction 2 times a day, and (4) providing the nutritional and water requirements in a way similar to any healthy child but at fixed time intervals.

Conclusions: This plan of management showed good effectiveness in controlling plasma sodium level and volume status of a child with adipsic DI without interfering with his average growth. This home treatment method is practical and readily available, provided that the family remains very adherent.

Keywords: Adipsia • Diabetes Insipidus • Thirst • Water-Electrolyte Balance

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Background

Normal cellular functions require adequately maintained tonicity of extracellular fluids within a very narrow range [1]. Serum electrolyte and water homeostasis is kept within the normal range by a coordinated interaction between thirst, arginine vasopressin (AVP) [or antidiuretic hormone (ADH)] release and action, and renal systems response [2]. Failure of any of these systems can result in an unfavorable environment for human cells, which, if not promptly recognized and treated, can cause life-threatening cellular dysfunction. Diabetes insipidus (DI) is a clinical syndrome characterized by polyuria, polydipsia, and, if not ameliorated by consuming enough water, hypernatremia. DI results from either impaired release of AVP, central DI, or resistance to the action of ADH, nephrogenic DI. Adipsia, a condition characterized by the lack of thirst sensation, usually occurs due to a central lesion that causes dysfunction of the thirst center in the hypothalamus [3]. In otherwise healthy individuals with DI, the thirst system can maintain plasma osmolality in the near-normal range despite relative AVP deficiency or decreased action [4]. In patients with DI who have normal cognition and free access to water, true hypernatremia (plasma sodium concentration >150 mmol/L) should not occur given that the initial water loss stimulates thirst, resulting in increased water consumption that matches urinary losses [5,6]. However, in cases where DI presents with adipsia, cognitive impairment, or restricted access to water, true hypernatremia can occur, leading to severe morbidity and mortality. Only around 100 cases of adipsic DI have been reported worldwide over the last 4 decades [7]. As such, there is indeed very limited experience in the management of such patients, especially children.

This report describes the clinical presentation and management provided, as well as the current understanding regarding adipsic DI.

Case Report

Our patient was a 2-year-old boy who had global developmental delay following a normal delivery after an uneventful pregnancy. He developed seizures starting on the third day after delivery. Initial brain magnetic resonance imaging (MRI) at the age of 2 months showed normal findings. At the age of 6 months, brain MRI showed a progressive, large, suprasellar thalamic, hypothalamic, and optic pathway tumor. Histopathological and molecular tests subsequently confirmed the tumor to be a low-grade diffuse glioma that affected cerebrospinal fluid flow, for which a ventriculoperitoneal shunt was inserted. The patient was then started on chemotherapy and his basal endocrine pituitary profile was normal: thyroid-stimulating hormone, 5.3 mIU/L; free thyroxine, 17.2 pmol/L; adrenocorticotropic hormone, 4.7 pmol/L; cortisol, 427 nmol/L; growth hormone, 44 mIU/L; insulin-like growth factor-1, 6.7 ng/mL; plasma osmolality: 278 mOsm/Kg, and urine osmolality: 323 mOsm/Kg). Initial serum electrolytes were normal, while urine output was within the normal range for his age. Although the patient was underweight, this could be explained by his chronic illness and recurrent admissions. Follow-up brain imaging showed progression of the brain lesion. Given that the patient was 2 years old, the attending team decided to perform debulking surgery. While the patient was awaiting surgery, he was presented to the emergency room for shunt malfunction. Thereafter, craniotomy, suprasellar lesion debulking, and external ventricular drain insertion were performed. After the surgery, the patient developed hypernatremia for 2 days (Figure 1), which was managed with intravenous (IV) vasopressin. Thereafter, the patient’s sodium level remained at borderline for 3 days (mixed DI and cerebral salt wasting [CSW]), during which urine sodium exceeded 300 mmol/L with polyuria above 20 mL/kg/h, which was managed with IV vasopressin and sodium replacement (through hypertonic saline infusion). The patient then exhibited hyponatremia for 10 days (a mixed syndrome of inappropriate secretion of ADH and CSW), during which urine sodium exceeded 300 mmol/L with normal admissions.

![Figure 1. Plasma sodium during the observation time](image-url)
including oral hydrocortisone (physiological replacement) that ating sodium levels. Other endocrine management procedures was genuinely challenging given the rapidly fluctu ing serum osmolality that reached 355 mOSM/kg. Furthermore, he was developing dehydration very rapidly whenever he had a urine output, which was treated by fluid balancing and sodi um replacement. Finally, the patient developed hypernatremia on day 15, which was managed with sublingual desmopressin (also known as DDAVP, which stands for 1-deamino-8-D-argi nine vasopressin) and fluid balancing. Initially, the patient was receiving 30 µg of sublingual DDAVP melt tablets twice daily, which was then increased to 30 µg in the morning and 60 µg in the evening. A dose of 60 µg twice daily caused water retention and hypernatremia. The patient never showed any sign of asking for water throughout his postoperative hospital stay despite ris ing serum osmolality that reached 355 mOSM/kg. Furthermore, he was developing dehydration very rapidly whenever he had a urinary breakthrough for as short a period as 2 h, but would exhibit hypervolemia and hypernatremia when given extra doses of DDAVP to prevent urinary breakthroughs. Overall, adjusting the DDAVP dose was genuinely challenging given the rapidly fluctu ating sodium levels. Other endocrine management procedures included oral hydrocortisone (physiological replacement) that has been started after prolonged high-dose dexamethasone ad ministration to reduce intracranial pressure. The patient had no symptoms of hypothyroidism except for low body temperature, which was attributed to the malfunction of the hypothalamic thermostat as a complication of extensive debulking surgery.

Guide to management (A unique table was designed to guide our progress; Figure 2)

1. Fixed DDAVP dosing that allows minimal urinary breakthroughs:
   - We provided fixed doses of sublingual desmopressin melt tablets twice daily: 30 µg in the morning and 60 µg in the evening. This dose regimen was the maximum dose that al lowed some urinary breakthroughs. The benefit of urinary breakthroughs is to prevent hypervolemia and hypernatremia given that fluid replacement is much easier than man aging volume overload.
2. Timely diaper weight-based replacement:
   • Input and output were always strictly monitored, with the allowed urine output being 4 mL/kg/h or less (for a 4-h period: 16 mL/kg or less). This cut-off number came from the definition of polyuria, which is defined as urine output above 2 L/m²/day [8]. For our patient, whose body surface area was 0.5 m², he would have polyuria if he had a urine output of 4.1 mL/kg/h, which was rounded to 4 mL/kg/h.
   • Urine output was being monitored every 4 h by weighing the diaper. Any volume exceeding the allowed urine output (ie, 4 mL/kg/h) was replaced by free water within the next 4 h.
   • If the diaper contained loose stool, similar management as with urine was provided. If the diaper contained hard stool, its weight could be estimated and subtracted.

3. Bodyweight-based fluid correction twice daily:
   • Given the normal growth and weight gain of the child, the expected changes in body weight should not be more or less than 2% of the previous weight. A gain or loss of more than 2% indicates water excess or deficit and hence hypernatremia or hyponatremia.
   • Measuring the weight of the child twice daily provides evidence of volume overload or depletion, which can then be corrected.
   • The following details our procedure for weight correction: The target serum sodium level was 140 mmol/L. The sodium serum level would be increased or decreased by 1 mmol/L for every 4 mL/kg of free water the patient lost or received [9]. Given that our patient weighed 10 kg, consuming 40 mL of sodium-free water would decrease the sodium serum level by 1 mmol/L, while consuming 400 mL would cause a reduction of sodium level by 10 mmol/L. Any gain or loss exceeding 2% body weight would prompt the subtraction (or addition) of the excess amount from the planned replacement by the next 4 hours.

4. Nutritional and water requirements similar to any healthy child but at fixed time intervals:
   • Total fluids and dietary requirements for the patient were calculated by a dietician based on the body weight to be given as fixed boluses at fixed time intervals (our patient was being given a bolus every 4 h, considering his young age, staying in the hospital, and dependence on non-solid foods).

5. Family and caregiver education:
   • The family and caregivers were willing to be adherent to the treatment plan and were taught until they showed complete understanding and were capable of practicing the regimen independently.

Follow-up

We used daily serum sodium levels, which normally lies between 135-145 mEq/L, as an indicator of successful management. Moreover, clinical indicators included daily clinical assessment of hydration status, fluid input and output, and twice-daily body weight monitoring. By utilizing the aforementioned method during his stay and the follow-up in day care unit for chemotherapy for more than 3 months, our patient no longer developed dehydration and had consistently normal serum urea levels, which means a good hydration status and, hence, a normal kidney function. Furthermore, the family was satisfied with this management approach. Although the follow-up to date is relatively short-term, he showed a normal growth pattern over the observation period. The patient was receiving weekly doses of chemotherapy. He also has been admitted 2 times for chest infections (Figure 1) when he was developing hypernatremia due to disturbance in his tight fluid management secondary to tachypnea and being on nil per os (NPO) state.

Discussion

Maintaining plasma osmolality and intravascular volume requires a concerted effort between thirst, AVP, and kidney function, in addition to a recently discovered bioactive peptide, aperelin, which has been isolated from bovine stomach extracts and is thought to play a key role in maintaining body fluids [2,10].

AVP is encoded by the AVP-neurophysin II gene (AVP-NPII) at the short arm of chromosome 20 (20p13) [11], while its secretion is regulated by osmotic and non-osmotic factors. Osmotic regulation of AVP release involves plasma osmolality sensing by the hypothalamic osmoreceptors, which are specialized neural osmoreceptors in the anterolateral hypothalamus responsible for AVP production and secretion. On the other hand, non-osmotic regulation of AVP release involves hemodynamic factors (ie, the renin-angiotensin-aldosterone and natriuretic peptide systems), nausea, and other regulators such as stress and drugs (eg, morphine, vincristine, cyclophosphamide, and glucocorticoids) [12].

The thirst sensation is triggered by peripheral osmoreceptor neurons in the upper regions of the gastrointestinal tract (GIT) and in blood vessels that collect nutrients absorbed from the GIT, as well as the central osmoreceptor located in the organum vasculosum of the lamina terminalis in the brain. Signals derived from peripheral osmoreceptors reach the brain through fibers that ascend the vagus nerve and spinal cord. Signals derived from both sources are then integrated in several brain areas [13].

Extracellular fluid osmolality is typically maintained at between 280 and 295 mOsm/kg H₂O in the general population [14], below which serum AVP levels are low or undetectable. Any increase in plasma osmolality above the 283 mOsm/kg H₂O threshold stimulates the release of AVP, which can also be
released in response to other AVP regulators, namely, the renin-angiotensin-aldosterone system, the natriuretic peptide system, and nausea [12]. However, the continued increase in plasma osmolality above 293 mOsm/kg H$_2$O despite AVP secretion triggers thirst, which in turn stimulates water ingestion to restore plasma volume [4], although this osmolar threshold for thirst varies among individuals [15].

In patients with DI (either central or nephrogenic), the absence or resistance to AVP action makes the thirst mechanism the first layer of protection against high plasma tonicity (thirst is first!). However, this mechanism by itself can maintain plasma osmolality at near-normal levels. The kidneys can accommodate up to 5 to 10 L/m$^2$ of water ingested under thirst drive during complete or relative AVP deficiency or resistance [4]. For this reason, most otherwise healthy individuals with DI are eunatremic and need a water deprivation test for diagnosis. On the other hand, patients with DI who have adipsia, cognitive impairment (eg, during a sedated state following surgery), or restricted access to water are at high risk for developing hypernatremia and, hence, life-threatening abnormalities in plasma osmolality unless they are closely monitored and promptly treated. The management of patients with adipsic DI is exceptionally challenging considering their inability to sense rising osmolality and their rapid, wide swings in plasma sodium and volume status. Treatment success, therefore, requires close observation, frequent reassessment of water balance, and an adherent family. Regarding the timely urine output measurements; the 4-h timing may be appropriate for admitted young patients, but should be spaced longer if the patient is old enough to withstand longer fasting, outside the hospital, and can consume solid foods.

To date, no practical guideline has been available for the treatment of cases with adipsic DI. Expert opinion, mainly for adult patients, suggests fixed doses of DDAVP to achieve a daily urine output between 1.5 and 2 L, daily water intake based on adjustments for daily weight changes on a 1 kg=1 L basis, and weekly monitoring of sodium levels [7]. These recommendations, however, are not suitable for pediatric patients considering their different physiological needs and relatively greater total body water content compared to adults, making them more sensitive to changes in extracellular compartment volume [16]. Furthermore, as children grow, their target weight can change over time.

Some pediatric endocrinologists have prescribed a home sodium monitoring device for patients with adipsic DI in combination with a sliding-scale fluid prescription plan, with an 84% success rate in maintaining plasma sodium at the reference range [17]. Unfortunately, this device is not always available. Moreover, the 84% success rate achieved in the aforementioned study is subject to many issues regarding accuracy, frequent blood sampling, and availability of consumables, while still being lower than our goal of 100% control. Pabich et al. managed a 16-year-old patient with fixed daily doses of subcutaneous DDAVP combined with daily modulation of fluid intake based on daily serum sodium measurement, which led to a reduction in hospitalizations resulting from the serum sodium dysregulation [18]. Again, the daily sodium measurement is not an available choice at all times and is not always practical, especially in young children. This led us to devise an easier and more practical way to manage the condition based on the physiology of the body fluids, having known the difficulties and limitations of the other modalities of management and trying to avoid daily blood sampling.

**Conclusions**

We present a new method for the management of adipsic DI in a pediatric patient. Overall, the main guidelines include (1) fixed DDAVP dosing that allows minimal urinary breakthroughs; (2) timely diaper weight-based replacement; (3) bodyweight-based fluid correction twice daily, and (4) nutritional and water requirements similar to those of any healthy child, but at fixed time intervals. This plan showed good effectiveness in controlling the plasma sodium level and volume status of a child with adipsic DI without interfering with his average growth throughout follow-up for 3 months. The main limitations were the absence of practical guidelines in the literature for the management of such cases, and difficulties regarding frequent fluids and weight measurements for the parents. As it does not require daily serum sodium measurements, this method of treatment is more practical and available, provided that the family remains very adherent. However, this proposed method still needs data on more patients before it can become standard of care.

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**Declaration of Figures’ Authenticity**

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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