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CASE REPORT

Diabetes insipidus uncovered during conservative management of complicated acute appendicitis

Anita Mamtani[1], Stephen R. Odom[1] & Kathryn L. Butler[2]

[1]Beth Israel Deaconess Medical Center, Department of Acute Care Surgery, 110 Francis St Suite 2G, Boston, Massachusetts, USA 02215
[2]Division of Trauma, Emergency Surgery & Surgical Critical Care, Massachusetts General Hospital, Boston, Massachusetts

Correspondence
Kathryn L. Butler, Division of Trauma, Emergency Surgery & Surgical Critical Care, Massachusetts General Hospital, 165 Cambridge Street, Boston, MA 02214.
Tel: +1-617-726-2760;
Fax: +1-617-724-0405;
E-mail: klbutler@partners.org

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Key Clinical Message

Diabetes insipidus (DI) arises from impaired function of antidiuretic hormone, characterized by hypovolemia, hypernatremia, polyuria, and polydipsia. This case is a reminder of the rare but challenging obstacle that undiagnosed DI poses in fasting surgical patients, requiring prompt recognition and vigilant management of marked homeostatic imbalances.

Keywords

Antidiuretic hormone, desmopressin, diabetes insipidus, perioperative.

Introduction

Diabetes insipidus (DI) arises from dysfunction in the interactions between antidiuretic hormone (ADH) and vasopressin receptors in the kidney. This dysregulation impairs a patient's ability to maintain physiologic free water levels, and causes significant homeostatic imbalances from massive polyuria, volume depletion, accompanying compensatory polydipsia, and marked hypernatremia. The syndrome may be central or nephrogenic. We describe a case of previously undiagnosed diabetes insipidus unmasked by periprocedural fasting in a patient with ruptured appendicitis. We outline her management and subsequent recovery, and discuss the background and management of DI, as well as the rare but important consideration of this diagnosis for surgeons in the perioperative period.

Description of Case

A 51-year-old previously healthy female presented to the Emergency Department with 4 days of worsening right lower quadrant pain, with intermittent nausea, vomiting, anorexia, and chills. She was found to have a leukocytosis of 15.0 K/μL; her basic metabolic panel was normal, including a sodium level of 146 mEq/L. CT scan revealed ruptured appendicitis, with an associated 8 × 3 × 3 cm abscess. She was admitted for intravenous antibiotics and percutaneous drainage of the fluid collection.

She was admitted in the late evening with percutaneous drainage scheduled for the following morning. Per routine, she was made NPO (*nil per os*) at midnight on the day of the procedure. She was noted to develop a progressive hypernatremia, hypokalemia, and hyperchloremia. Only 18 h after being made NPO, her sodium peaked at 180 mEq/L (normal: 133–146 mEq/L), chloride peaked at 137 mEq/L (normal: 96–108 mEq/L), and potassium was as low as 2.7 mEq/L (normal: 3.3–5.1 mEq/L). She had a rapid diuresis, with an average urine output of 500–600 cc/h. At this time, urine osmolality measured 240 mOsm/kg, and urine specific gravity was 1.003. The trend of her plasma sodium, plasma osmolality, and urine osmolality is depicted in Table 1. She was clinically asymptomatic.

Upon further discussion, the patient endorsed severe thirst, stating that she drank >12 cups of water per day

Table 1. Chronological trend of sodium plasma, sodium osmolality, and urine osmolality before and after diagnosis.

Sodium (plasma) Normal: 133–144 mEq/L	Osmolality (plasma) Normal: 275–310 mOsm/kg	Osmolality (urine)
146	Not checked	Not checked
163	359	94
178	360	144
180	**365**	**240**
Diagnosis made and treatment initiated		
176	358	140
160	351	132
150	298	116
142	285	110

Bold values indicate peak levels prior to treatment.

since childhood, often waking throughout the night to do so. She also reported a long-standing history of urinating every 2 h. She had never before been hospitalized or restricted from her usual water intake. She was evaluated by Endocrinology, and transferred to the intensive care unit for closer monitoring. She was given 10 mcg of intranasal desmopressin (DDAVP), followed by 2 mcg of subcutaneous DDAVP, with a marginal decrease in urine output. Slowly increasing doses of IV DDAVP were given, and titrated up to 4 mcg IV DDAVP every 6 h. Throughout this process, hourly monitoring of serum sodium, urine osmolality, and urine specific gravity was performed. Urine output was matched with intravenous free water (D5W), and resultant hyperglycemia was managed with an insulin drip, to prevent osmotic diuresis and further loss of free water. Her moderate response to this regimen was suggestive of a central DI, but to investigate a potential nephrogenic component, a hydrochlorothiazide (HCTZ) trial was also done, to which she displayed an insignificant response.

After 3 days of this treatment and meticulous monitoring, her sodium level improved to 142 mEq/L. She underwent uncomplicated percutaneous drainage of her abscess, from which cultures grew S*treptococcus anginosus*. Postprocedurally, 0.2 mg oral DDAVP twice daily was started, and her diet was advanced. She was discharged on this regimen, along with a 10-day course of oral Augmentin for her appendicitis. On follow-up, she reported drinking much less water. Uncomplicated interval appendectomy was performed 2 months later, after preoperative admission for endocrine optimization, and overnight close monitoring of sodium levels while NPO, with ddAVP administration.

Further investigation of the etiology of this patient's DI proved complex. Originally, it was felt that she had central DI given good response to ddAVP, minimal response to HCTZ, resolution of symptoms, and improvement in laboratories. While an MRI of the pituitary could not be obtained due to patient having a metal-containing intra-uterine device, a CT sella and correlating hormone levels for all relevant hormone axes suggested a nonfunctioning 4-mm pituitary microadenoma. Measured hormone levels included: FSH 4 mlU/mL (normal: 2–12 mlU/mL), LH 23 mlU/mL (normal: 2–100 mlU/mL), prolactin 23 ng/mL (normal: 5–23 ng/mL), TSH 2.7 μlU/mL (normal: 0.27–4.2 μlU/mL), IGF-1 123 ng/mL (normal: 50–317 ng/mL), and cortisol 12.7 μg/dL (normal: 2–20 μg/dL). Investigative laboratory work for granulomatous disorders was also unrevealing. Two months thereafter, the patient reported that although improved from presentation, she had once more developed polyuria and polydipsia, despite continuation of ddAVP. She was found to have residual hypernatremia, and more erratic urine osmolality than at time of ddAVP initiation. This raised suspicion for a variant congenital nephrogenic DI, and the likelihood that her initial response to ddAVP may have been amplified due to the higher doses administered while hospitalized. Genetic testing ultimately showed her to be a carrier for a variant AVPR2 mutation. A unique DI-causing X-linked missense mutation, this determined the true etiology of her disease to be nephrogenic. She was transitioned from ddAVP to HCTZ thereafter, and has since had full resolution of both her symptoms and laboratory abnormalities.

Discussion

Diabetes insipidus is a manifestation of inadequate water conservation to maintain a physiologic free water level [1]. This is due to a dysfunction in the interactions of antidiuretic hormone and the vasopressin receptors in the kidney, causing a dilute water loss and resultant hypernatremia. This syndrome may be either central or nephrogenic. Central DI is due to inadequate production of functional antidiuretic hormone, caused by congenital or acquired infiltrative processes, neoplasm, autoimmune diseases, surgery, or trauma. Nephrogenic DI, however, is more often due to mutation of protein components of the antidiuretic hormone itself, or of the vasopressin receptors, resulting in absent or decreased function in the kidney. This may also be caused by either congenital or acquired means, including infiltrative diseases, neoplasm, or autoimmune disorders [1, 2]. In a chronic state of disease, an adaptive mechanism of compensatory thirst and significantly increased oral water intake is seen.

Undiagnosed DI may be unveiled during fasting prior to surgery or procedures involving the administration of sedation. The resultant massive diuresis, hypotension, and hypernatremia may present unexpectedly, and requires prompt recognition and careful management [3]. In the surgical realm, this has been very rarely reported, with

only a few case reports specifically in the postoperative setting after kidney transplantation [4]. These patients, distinct from our patient case, were not able to manifest DI while anuric, but developed the biochemical and clinical manifestations of DI after the placement of a successful renal allograft [4].

A combination of hypernatremia of greater than 160 mEq/L, a plasma osmolality greater than 290 mOsm/kg, a urine osmolality of less than 200 mOsm/kg, and a significant polyuria are suggestive of DI. The marked hypernatremia is the most immediately concerning imbalance, particularly in the perioperative setting. Symptoms of hypernatremia can include altered mental status, confusion, dysarthria, muscle tremor/rigidity, and potentially life-threatening coma. Any major procedure or operation cannot be safely performed unless sodium is corrected and DI is controlled. The dramatic alterations in intravascular volume can lead to profound hypotension; hypernatremia will also increase the minimum alveolar concentration of inhaled anesthetic agents. Furthermore, there is concern for altered requirements of local anesthetics in hypernatremia, and an exaggerated depressant effects of opioids.

Acute management includes treatment of the hypernatremia itself, while also providing appropriate volume repletion for losses in urine. Close monitoring of changing serum sodium and urine osmolality, and prevention of osmotic diuresis from hyperglycemia concomitant to intravenous free water (D5W) replacement are paramount. Rapid sodium correction is hazardous, particularly due to the risk of cerebral edema from rapid reduction in serum osmolality. To avoid neurological injury, the serum sodium level should be reduced by no more than 0.5 mmol/L per hour [1]. Most importantly, management of central DI must include correction of the central deficit, by providing exogenous desmopressin [2]. Should there be concern for a nephrogenic component, thiazide diuretics and nonsteroidal anti-inflammatory drugs may be trialed. Thiazide diuretics act by inducing a mild hypovolemia resulting in proximal sodium and water reabsorption, thereby diminishing water delivery to distal ADH-mediated sites in the nephron. NSAIDs increase concentrating capability through the ADH-antagonizing action of prostaglandins. In both types of DI, the long-term aim of therapy is to maintain a biochemical homeostasis, and thereby alleviate symptoms of polyuria, nocturia, and polydipsia.

Determination of the exact etiology of DI is important to optimize medical management of the disease process. As seen in our patient, this may prove complex, generally involving imaging of the pituitary, investigation of relevant hormone axes, trial of specific nephron receptor-directed therapies, and genetic testing. The AVPR2 (arginine vasopressin receptor 2) gene is located on the X-chromosome, and codes for the vasopressin V2 receptor. This is a receptor for ADH expressed in the distal convoluted tubule and collecting ducts of the nephron, responsible for stimulating mechanisms for urine concentration and water hemostasis when activated. More than 200 different mutations in the AVPR2 gene have been identified. These mutations lead to the production of dysfunctional or inadequate vasopressin V2 receptor proteins, and are responsible for approximately 90% of cases of nephrogenic DI [5]. A more rare polymorphism was seen in our patient, a missense mutation manifesting a "skewed X inactivation" principle in which females who are heterozygous for an AVPR2 mutation have symptoms similar to that of a homozygous male [5]. Her initial paradoxical improvement with ddAVP may potentially have been due to an amplified response of dysfunctional vasopressin V2 receptors to exogenously provided ddAVP, but proved to be a short-lived phenomenon, with recurrence of symptoms thereafter.

This case was a reminder of the rare but potential treatment obstacle that previously undiagnosed DI may pose in the perioperatively fasting surgical patient. Compensatory polydipsia is disrupted during perioperative fasting and requires vigilance in monitoring and management. This case also highlights the importance of prompt recognition and treatment, clear identification of the exact etiology of the disease process, and the benefits of maintaining a heightened suspicion in surgical patients.

Conflict of Interest

None declared.

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