Clinical Presentation

A 37-year-old nulligravid woman known to have polycystic ovarian syndrome, depression, and back pain secondary to a remote car accident was admitted to the hospital for lumbar spine fusion to relieve her back pain. Preoperative laboratory values were unremarkable. Home medications included hydrochlorothiazide, 25 mg, daily; duloxetine, 60 mg, twice daily; aripiprazole, 10 mg, daily; and clonazepam, 0.25 mg, daily. Surgery was performed under general anesthesia, the procedure was uneventful, and she was maintained on maintenance fluids with 0.45% saline and 5% dextrose solution at 75 mL/h perioperatively. On postoperative day 1, the patient was found to be agitated and confused and was reporting intense thirst.

On physical examination, vital signs were notable for temperature of 36.4°C, heart rate of 104 beats/min, blood pressure of 134/78 mm Hg, respiratory rate of 14 breaths/min, and oxygen saturation of 100% while breathing room air. Mucous membranes were dry, cardiac examination findings were unremarkable except for tachycardia, lungs were clear to auscultation, abdomen was soft and nontender, and extremities were without edema. The surgical incision was cleanly opposed without erythema or fluctuance. Serum sodium concentration [Na] was noted to be elevated to 152 mEq/L. Urine output was not recorded, but urinalysis showed a urine specific gravity of 1.005.

Discussion

What is the differential diagnosis of hypernatremia in this patient?

Hypernatremia is defined as [Na] > 145 mEq/L. [Na] is determined by the relationship between the major exchangeable extra- and intracellular cations according to the formula: [Na] = (total-body exchangeable sodium + potassium)/total-body water. Hypernatremia is most commonly the result of total-body water deficit. However, other less common causes of hypernatremia should be considered as well (Fig 1). Total-body water deficit or excess sodium administration can lead to hypernatremia in hospitalized patients who concomitantly have an impaired thirst mechanism or in patients with intact thirst but who have compromised access to water.

Our patient was somnolent following general anesthesia in the postoperative period, limiting her access to free water for 12 hours. No hypertonic fluids or salt tabs were administered, and no gastrointestinal losses were reported. This short period of restricted free water access should not increase [Na] significantly unless there is a concomitant water loss. Urine osmolality of 129 mOsm/kg confirmed the diagnosis of diabetes insipidus (DI).

What laboratory testing would help establish the diagnosis?

The patient was given 4 μg of desmopressin intravenously. Copious urine output continued, and urine osmolality at 2 hours was 155 mOsm/kg. Therefore, according to the principles of the water deprivation test (Fig 2), a diagnosis of nephrogenic DI was made.

Although the water deprivation test is the classic diagnostic test for distinguishing different causes of polyuria, this method is fraught with limitations, particularly because prolonged polyuria washes down the medullary gradient and downregulates aquaporin 2 channels, therefore limiting urinary concentration.

Recently, a copeptin-based approach to differentiate between the various forms of hypotonic polyuria has been found to be superior to the water deprivation test. Copeptin is the carboxy-terminal segment of the arginine vasopressin (AVP) prohormone. Copeptin is released into the circulation with AVP, but has no defined biological role. It remains stable in circulation and is easier to measure than AVP, making it a good surrogate for AVP levels. Copeptin measurement following a 3% hypertonic saline solution infusion that increases [Na] to 150 mEq/L has 96.5% (95% confidence interval [CI], 92.1%-98.6%) overall diagnostic accuracy (with 93% sensitivity and 100% specificity) in discriminating different causes of hypotonic polyuria. This is superior to the diagnostic accuracy of the water deprivation test of 76.6% (95% CI, 69.9%-83.2%).
What is the likeliest underlying cause of this patient’s condition?

The patient was rehydrated with 5% dextrose in water intravenously followed by oral fluid intake when her sensorium cleared. On further questioning, she reported having infantile seizures from “dehydration.” She had experienced frequent urination and large water intake her whole life and had been taking hydrochlorothiazide to decrease her urine output since childhood. In her teens, she was admitted to the hospital for overnight water deprivation test.

Figure 2. Water deprivation test for the differentiation between central diabetes insipidus (DI) and nephrogenic DI.

Figure 1. Causes of hypernatremia. It is important to note that the development of hypernatremia due to water losses almost always requires the concomitant presence of impaired water intake.
AQP2 and are largely caused by milial cases of nephrogenic DI are autosomal recessive. The AVPR2 gene encodes the AVP receptor. Approximately 10% of familial cases of nephrogenic DI are autosomal recessive, and are largely caused by AQP2 gene mutations. AQP2 is located on the long arm of chromosome 12 at position 13.12 and encodes the aquaporin 2 channels in the collecting tubule. The incidence of hereditary nephrogenic DI caused by AQP2 mutation is around 1 in 20 million births. The remaining 1% or so of nephrogenic DI is due to autosomal dominant mon- orallelic mutations in the AQP2 gene. The dominant form is generally the least severe of the familial forms because patients have less resistance to AVP compared with other forms.

The patient had no family history of DI and her father and maternal grandfather had been healthy, making X-linked disease unlikely. Her parents were not known to be related but both came from a remote sparsely populated town in the Caribbean. This history raised suspicion for autosomal recessive disease. Thus she underwent targeted genetic testing of AQP2 (Table 1), which revealed a homozygous duplication of a thymidine at nucleotide 576 of the coding sequence (c.576dupT), which is predicted to lead to a loss-of-function frameshift, p.(Val193CysfsTer7). This confirmed the diagnosis of autosomal recessive DI due to AQP2 mutation.

**What is the most effective therapy for this condition?**

The recommended treatment of nephrogenic DI includes a low-sodium diet and thiazides, except in lithium-induced nephrogenic DI, for which amiloride is the preferred agent. Hydrochlorothiazide reduces sodium reabsorption at the distal convoluted tubule, leading to extracellular volume contraction, which in turn stimulates proximal tubular sodium and water reabsorption. This leads to lower sodium delivery to the distal and collecting tubules and as such, less water excretion. This mechanism explains the short-term effect of thiazides. In the long term, thiazides upregulate aquaporin channels, the sodium chloride cotransporter, and the epithelial sodium channel. The increase in sodium chloride cotransporter and epithelial sodium channel enhances distal tubular sodium reabsorption, leading to less water excretion.

In this patient, the combination of withholding her hydrochlorothiazide perioperatively and volume expansion with maintenance fluids acutely increased renal electrolyte-free water excretion. This, combined with an inability to drink perioperatively, resulted in her acute hypernatremia. The patient had not emphasized her condition to the clinical team before her routine surgery because, in her words, “it’s how I’ve been my whole life.” Had the team been aware of her condition preoperatively, appropriate management would have included more aggressive hydration with hypotonic fluids and careful monitoring of both urine output and serum osmolality, potentially avoiding the development of hypernatremia. The patient was restarted on hydrochlorothiazide therapy with reported improvement in polyuria and with stable normal serum sodium.

**Final Diagnosis**

Congenital nephrogenic diabetes insipidus secondary to AQP2 mutation.

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**Quiz**

**Table 1. Summary of Molecular Genetic Testing Used in Nephrogenic Diabetes Insipidus**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genetic Testing</th>
<th>Comments</th>
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<tbody>
<tr>
<td>AVPR2</td>
<td>• Sequence analysis to detect sequence variants</td>
<td>• AVPR2 mutations account for 90% of NDI cases</td>
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<tr>
<td></td>
<td>• Deletion/duplication analysis to detect exon or whole-gene deletions/duplications</td>
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</table>

Abbreviation: NDI, nephrogenic diabetes insipidus.
Based on information presented in Adam et al in GeneReviews.

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Aggressive intravenous fluid repletion for food poisoning. Despite having no family history, the early onset of symptoms suggested a genetic cause of nephrogenic DI.

Hereditary nephrogenic DI is transmitted in an X-linked recessive mode in 90% of cases. It is most commonly due to mutations in the AVPR2 gene, which encodes the AVP receptor. Approximately 10% of familial cases of nephrogenic DI are autosomal recessive and are largely caused by AQP2 gene mutations. AQP2 is located on the long arm of chromosome 12 at position 13.12 and encodes the aquaporin 2 channels in the collecting tubule. The incidence of hereditary nephrogenic DI caused by AQP2 mutation is around 1 in 20 million births. The remaining 1% or so of nephrogenic DI is due to autosomal dominant mon- orallelic mutations in the AQP2 gene. The dominant form is generally the least severe of the familial forms because patients have less resistance to AVP compared with other forms.

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References

FELLOWSHIP PROGRAM HIGHLIGHT

Note from editors: To recognize fellowship programs’ educational mission, AJKD is using its popular Quiz feature to highlight Nephrology Fellowship programs when an author is a Nephrology Fellow. To participate, Fellowship Program Directors mentor fellows in submitting prospective Quizzes; those that are selected for publication include a brief description of the fellowship program from the Director. For “A Case of Iatrogenic Dehydration,” the corresponding author is Pascale Khairallah, who at the time of manuscript submission was a Postdoctoral Clinical Fellow at Columbia University.

Program: New York Presbyterian Hospital-Columbia University Medical Center (http://columbianephrology.org/index-13.shtml)

Program Director: Pietro Canetta, MD

Program Description from Dr Canetta: The nephrology fellowship program at New York Presbyterian-Columbia University Medical Center carries on a long tradition of excellence in nephrology training. We are a traditional 2-year program with 3 to 4 fellows per class, each following either a clinical or research track. The program is designed to provide outstanding practical and academic training in every aspect of nephrology. Our environment is thoroughly academic, with ample opportunities to engage in clinical and translational research, supported by a National Institutes of Health–sponsored T32 grant. Fellows regularly enter a fully funded Masters program in patient-oriented research at our School of Public Health. Fellows also have access to formal training or exposure to advanced subspecialties, including glomerular disease, kidney transplantation, personalized medicine, bioinformatics, interventional nephrology, and critical care.

Submitting a Manuscript for Consideration

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