Ms. V, age 58, presents to the emergency department after falling in the middle of the night while walking to the bathroom. Her medical history includes bipolar I disorder (BDI). According to her granddaughter, Ms. V has been stable on lithium 600 mg twice daily for 1 to 2 years. Her laboratory workup shows a serum creatinine level of 0.93 mg/dL (reference range 0.6 to 1.2 mg/dL), high sodium (154 mEq/L; reference range 135 to 145 mEq/L), and a lithium level of 0.9 mEq/L (therapeutic range 0.6 to 1.2 mEq/L). On Day 2 of admission, Ms. V's sodium level remains high (152 mEq/L), her urine output is 5 L/d (normal output <2 L/d), and her serum osmolality is high (326 mmol/kg; reference range 275 to 295 mmol/kg).

After additional questioning, Ms. V says for the past 3 weeks she has been urinating approximately 4 times per night and experiencing excessive thirst. Given her laboratory values and physical presentation, a desmopressin challenge test is performed and confirms a diagnosis of lithium-induced nephrogenic diabetes insipidus (Li-NDI).

Nephrogenic diabetes insipidus (NDI) occurs when the kidneys become unresponsive to the action of antidiuretic hormone (ADH; also known as vasopressin). The most common cause of NDI is lithium. The prevalence varies from 50% to 73% with long-term lithium use. It is important to recognize the homeostatic regulation of water prior to understanding Li-NDI. The excretion of water is regulated by ADH. ADH binds to the vasopressin receptors on the basolateral membrane of the collecting duct cells. This stimulates Gs protein and adenylate cyclase, which subsequently increase intracellular cyclic adenosine monophosphate (cAMP). Eventually, this leads to the activation of protein kinase A and phosphorylation of aquaporin 2 (AQP2) water channels. The AQP2 channels redistribute from storage vesicles to the apical membrane and the membrane becomes permeable to water, allowing for reabsorption.
In Li-NDI, lithium enters the cells of the collecting duct through the epithelial sodium channel (ENaC). There, lithium inhibits the action of ADH, glycogen synthase kinase-3 (GSK-3) activity, and the generation of cAMP. It also induces cyclooxygenase-2 expression in renal interstitial cells and the production of prostaglandin E2 (PGE2). Lithium may also reduce the amount of AQP2 water channels in the apical membrane of the collecting duct. Additionally, polymorphisms of the GSK-3 beta gene can occur, which may be related to differences in the extent of the lithium-induced renal concentrating defect among patients who take lithium.

Symptoms of Li-NDI include polyuria (ie, urine production >3 L/day) and polydipsia. More than 40% of patients with symptomatic Li-NDI experience a significant interference with their daily routine and occupational activities, and may be at risk for severe dehydration with concurrent electrolyte disturbances, resulting in lithium toxicity. This could especially impact older adults, who may have a diminished thirst sensation and insufficient fluid intake (ie, psychological decompensation, decreased mobility).

Li-NDI is reversible early in treatment; however, it may become irreversible over time. The degree of reversibility depends on the extent of dehydration, electrolyte disturbances, and lithium toxicity.

### Table 1

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Normal</th>
<th>Abnormality seen in NDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine osmolality</td>
<td>1,000 mmol/L</td>
<td>&lt;100 mmol/L</td>
</tr>
<tr>
<td>Urine output</td>
<td>&lt;3 L/d</td>
<td>&gt;3 L/d; up to 18 L/d</td>
</tr>
<tr>
<td>Plasma osmolality</td>
<td>275 to 290 mmol/kg</td>
<td>&gt;290 mmol/kg</td>
</tr>
<tr>
<td>Arginine vasopressin level</td>
<td>0.9 to 4.6 pmol/L</td>
<td>&gt;4.6 pmol/L</td>
</tr>
</tbody>
</table>

NDI: nephrogenic diabetes insipidus

Source: Reference 10

### Table 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>5 mg/d to 20 mg/d; may divide into twice-daily dosing</td>
<td>Directly blocks lithium reuptake in the kidney; less likely to increase lithium levels; monitor for hyperkalemia</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>10 ug/d to 40 ug/d intranasal; may divide into 2 or 3 times daily dosing</td>
<td>Little data supporting use in Li-NDI; may be useful in Li-NDI with central diabetes insipidus component</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>50 mg/d to 150 mg/d; may divide into 2 or 3 times daily dosing</td>
<td>Most widely used agent; multiple mechanisms; increase in lithium levels; monitor for hypokalemia</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>100 mg/d to 150 mg/d; may divide into 2 or 3 times daily dosing</td>
<td>Consider use as adjunct; may potentiate ADH activity; increase in lithium levels; risk of acute renal failure</td>
</tr>
</tbody>
</table>

ADH: antidiuretic hormone; Li-NDI: lithium-induced nephrogenic diabetes insipidus
on the stage of kidney damage (ie, functional vs morphological) and/or duration of lithium treatment. Even with the discontinue of lithium, symptoms may persist. Imaging can be used to identify the extent of kidney damage, but given the inconsistent data regarding the reversibility of Li-NDI, it would be difficult to predict if symptoms will resolve.

Establishing the diagnosis
A physical examination and laboratory workup are the first steps in diagnosing and determining the underlying cause of NDI. Table 1 outlines common laboratory abnormalities associated with NDI. Additionally, serum sodium levels can be used to determine water balance; hypernatremia is often seen in cases of NDI. Water deprivation tests are useful for diagnosing diabetes insipidus and allow for differentiation of nephrogenic vs central diabetes insipidus. Once the patient is water-deprived for ≥4 hours, a single 3-unit dose of subcutaneous desmopressin may be administered. In Li-NDI, the urine often remains dilute with urine osmolality levels <200 mmol/kg, even after administration of exogenous arginine vasopressin.

Several treatment options
In many cases, Li-NDI symptoms can be reduced by using the lowest effective dose of lithium, switching to a once-daily formulation, or discontinuing therapy. Some patients may find relief from certain diuretics, such as amiloride. Thiazide diuretics can also be used but may require a ≥50% reduction in lithium dose. Nonsteroid anti-inflammatory drugs, such as indomethacin, in combination with diuretics, have been found to be effective by increasing the concentration of urine. Table 2 summarizes potential treatment options.

Amiloride has the most supporting evidence in the treatment of Li-NDI. A potassium-sparing diuretic, amiloride works by blocking the ENaC in the distal and collecting duct. Blocking the ENaC inhibits uptake of lithium into the principal cells of the collecting duct within the kidney. Research has shown that amiloride can be effective in treating existing Li-NDI, but there is a lack of evidence supporting its preventative effects.

Thiazide diuretics work by blocking the sodium-chloride cotransporter in the distal tubules of the kidney. They also upregulate the AQP2 water channels. Research has shown that sodium replacement counteracts the antidiuretic effect of thiazide diuretics; limitations in dietary sodium intake may be necessary for treatment efficacy.

Within the kidneys, PGE2 inhibits adenyl cyclase and diminishes water permeability. This causes water to be excreted in urine rather than be reabsorbed. Indomethacin blocks PGE2 activity and increases water reabsorption in the collecting ducts, and sodium reabsorption in the thick ascending loop of Henle. This mechanism can lead to increased lithium reabsorption, which may precipitate toxicity. Research has shown increases in lithium levels by as much as 59% in addition to the risk of causing acute renal failure, especially in older adults. Due to these risks, indomethacin should not be considered a first-line treatment for Li-NDI.

Overall, several medications have shown benefits in the treatment of Li-NDI, with amiloride having the most data. There are currently no medications with sufficient evidence to support prophylactic use.

Related Resources

Drug Brand Names
- Amiloride - Midamor
- Desmopressin - DDAVP
- Hydrochlorothiazide - Microzide
- Indomethacin - Indocin, Tivorbex
- Lithium - Eskalith, Lithobid

Clinical Point
Water deprivation tests can help differentiate nephrogenic vs central diabetes insipidus
Clinical Point

Although several medications can help treat Li-NDI, none have sufficient evidence for prophylactic use.

CASE CONTINUED

Ms. V’s treatment team initiates amiloride 5 mg/d. They increase the dose to 10 mg/d after 2 days, and Ms. V’s hypernatremia resolves as her serum sodium normalizes to 142 mEq/L. Her urinary output also decreases to <3 L/d. Throughout treatment, Ms. V continues taking lithium carbonate to prevent destabilization of her BDI. The team subsequently discharges her, and she has been stable for the past 6 months.

References