An 85-year-old man is found to have a serum sodium level of 128 mmol per liter during his annual evaluation. He has noted some “mental slowing” and gait instability. The patient’s history is notable for primary hypertension and prostatic hypertrophy. His medications include amlodipine, finasteride, and tamsulosin. His blood pressure is 136/68 mm Hg without orthostatic changes; the remainder of the examination is unremarkable. Repeat testing reveals a serum sodium level of 127 mmol per liter, osmolality of 260 mOsm per kilogram of water, creatinine level 0.8 mg per deciliter (70.7 μmol per liter), blood urea nitrogen level of 8 mg per deciliter (2.9 mmol per liter), and uric acid level of 4 mg per deciliter (0.24 mmol per liter). The urine osmolality is 645 mOsm per kilogram of water, and the sodium level is 95 mmol per liter. How should this patient be further evaluated and treated?
SYNDROME OF INAPPROPRIATE ANTI DIURESIS (SIAD)

- Hyponatremia is the most common electrolyte abnormality. The condition is usually caused by a water excess relative to sodium and potassium content.
- In SIAD, a frequent cause of hyponatremia, increased secretion of antidiuretic hormone in the absence of osmotic and hemodynamic stimuli leads to water retention by the kidneys and water excess.
- Manifestations of SIAD depend on the rapidity of development and the severity and duration of the condition. Symptoms range from mild and nonspecific (e.g., weakness and headache) to severe and life-threatening (e.g., seizures and coma).
- Causes of SIAD include cancer, medications, pulmonary conditions, disorders of the central nervous system, postoperative state, severe nausea, and stress; frequently the cause is undetermined.
- Severely symptomatic SIAD leads to emergency treatment with 3% sodium chloride to reverse cerebral edema. Consultation with a specialist is warranted.
- Management strategies for SIAD include reversal or amelioration of the underlying disorder when possible; fluid restriction; supplementation with sodium chloride, often with furosemide; and treatment with urea or tolvaptan.

The prevalence of hyponatremia overall, and of SIAD specifically, increases with age; 40% of older (>65 years of age) inpatients have hyponatremia, with 25 to 40% of cases attributed to SIAD. This increased prevalence is attributable to the frequent presence among older persons of coexisting conditions (e.g., cancer, pulmonary diseases, and disorders of the central nervous system [CNS]) and medications that predispose to SIAD. In addition, aging impairs aquarexia by means of diminished glomerular filtration rate, decreased renal prostaglandins, and increased AVP response to osmotic and nonosmotic stimuli; low salt and protein intake, common in older persons, also contributes to impaired aquarexia. Even a modest increase in water intake compounds the risk of hyponatremia.

Manifestations of SIAD depend on the rapidity of development and the severity and duration of hyponatremia. Symptoms of acute SIAD (<48 hours from onset of hyponatremia) result from cerebral edema and range from mild and nonspecific (e.g., weakness and headache) to severe and life-threatening (e.g., seizures and coma). Because brain-volume regulation reverses cerebral edema, symptoms of chronic SIAD (>248 hours from onset of hyponatremia) are commonly subtle, although severe chronic SIAD can be associated with nausea, vomiting, headache, confusion, delirium, and, rarely, seizures. Other manifestations associated with chronic SIAD, such as cognitive deficits, gait abnormalities, falls, osteoporosis, and fragility fractures, may be misattributed to normal aging.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The diagnosis of SIAD requires clinical confirmation of euvoletic hypotonic hyponatremia (Fig. 1). Given the low sensitivity and specificity of a physical examination in assessing volume status, European guidelines prioritize measurement of urine osmolality and sodium. Urine studies showing natriuresis (sodium, >30 mmol per liter) and inappropriate concentration (osmolality, >100 mOsm per kilogram of water) are consistent with SIAD. However, diagnosing SIAD requires ruling out secondary adrenal insufficiency and severe hypothyroidism. In practice, requisite serum and urine tests for diagnosis are often omitted; the Hyponatremia Registry showed that those tests were completed in only 21% of patients in whom SIAD was diagnosed. The causes of SIAD are numerous (Table 1). Major categories of causes (and relative frequencies) of SIAD included in the Hyponatremia Registry are cancer (24%), certain drugs (18%), pulmonary conditions (11%), and CNS disorders (9%). Additional causes are exercise, pain, stress, severe nausea, postoperative state, and, rarely,
gain-of-function variants of gene encoding vaso-
pressin 2 receptor (in nephrogenic SIAD).2–4
More than one cause is frequently present.12,21
Antidepressants are the most commonly impli-
cated drugs, especially in underweight older
women22; the risk relative to the use of antide-
pressants has been reported to be highest with
the use of selective serotonin-reuptake inhibitors
and lowest with mirtazapine. No cause is identi-
fied in 17 to 60% of patients with SIAD, depend-
ing on the extent of the evaluation and patient age
(occurrence is highest among older persons).21,23

Reversal of hyponatremia upon discontinua-
tion of a drug establishes the causal relation-
ship. In the absence of clinical diagnostic clues,
experts generally recommend computed tomog-
raphy (CT) of the head and chest; if imaging
results are negative, CT of the abdomen and pelvis may be considered.4

**Management**

**Emergency Treatment**

Urgent treatment is required for patients with
SIAD who have severe symptoms of hyponatre-
mia (e.g., somnolence, seizures, cardiorespira-
tory distress, or coma); moderately severe symp-
Most commonly observed in small-cell lung cancer (approximately 25% of the cases of SIAD that are gastrointestinal, genitourinary.

The situation of AVP by some cancers has been documented (e.g., small-cell lung cancer and its metastases and olfactory neuroblastoma); tumor regression can reverse SIAD.

Central nervous system

Develops in up to 56% of patients with subarachnoid hemorrhage and up to 35% of those with transcranial disorders (e.g., occurring during a postoperative state), adherence to correction limits is unnecessary. However, the duration of hyponatremia usually cannot be ascertained.

Drug-related

Stimulants of AVP release (e.g., opiates, ifosfamide, and platinum compounds), enhancers of AVP (e.g., SSRIs, haloperidol, carbamazepine, cyclophosphamide, and chlorpropamide), and stimulants (e.g., occurring during a postoperative state), adherence to correction limits is unnecessary. However, the duration of hyponatremia usually cannot be ascertained.

Other

Idiopathic

Widely variable prevalence (17 to 60% of cases), most commonly reported in older patients; occasionally, an apparent idiopathic case has later been found to have been caused by occult tumor.

Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIAD).

<table>
<thead>
<tr>
<th>Categories</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Pulmonary and mediastinal, nasopharyngeal, gastrointestinal, genitourinary, and repeated two or three times as needed.</td>
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tremia cannot be ruled out. Emergency treatment requires close monitoring, preferably in the intensive care unit, and consultation with a specialist (i.e., intensivist, nephrologist, or endocrinologist).  

A nonrandomized study involving patients with severe symptomatic SIAD who were treated with 100 ml of 3% sodium chloride administered as an intravenous bolus showed an increase in serum sodium levels that was greater than that observed in a historical comparison group in which patients received 3% sodium chloride in a continuous infusion (6 mmol per liter vs. 3 mmol per liter at 6 hours) and reported greater neurologic improvement in that time interval; overcorrection occurred in 4.5% of the patients who received sodium chloride by intravenous bolus as compared with none of the patients who received continuous infusion, and sodium-relowering therapy was used in 23% and 0%, respectively. Two other small studies also showed high rates of overcorrection (17% and 28%) and sodium-relowering therapy (41% and 28%) with the bolus approach (150 ml per dose); however, these studies included many participants with hypovolemia in whom aquaresis probably developed after volume repletion. 

Overcorrection can occur because of excessive administration of 3% sodium chloride owing to repeated fixed-dose boluses. The effects that a given dose has on the serum sodium level depend on the sodium level at baseline and the total body water (the latter affected by sex, weight, and body fat). An individualized approach to the administration of 3% sodium chloride can be applied with the use of a formula that effectively predicts the change in the serum sodium level after the infusion of 1 liter of any solution if there is no other input or output. The change from baseline in sodium level is calculated according to the following formula: (sodium+potassium) infusate–sodium level at baseline+total body water+1. The formula has been validated with regard to patients with SIAD who remain antidiuretic, with actual serum sodium levels at 24 hours that are very similar to predicted levels. 

Overcorrection can also occur because of transition to aquaresis (urine output, >100 ml per hour) after the discontinuation of causative drugs or reversal of transient SIAD (e.g., postoperative state). The effect of aquaresis on serum sodium can be quantitated by means of a simple fluid-loss formula. To counter such risk, desmopressin can be used proactively (anticipating aquaresis) or reactively (responding to aquaresis). However, randomized trials of desmopressin are lacking in these contexts; retrospective studies have shown no consistent benefit associated with its use and potential complications, including volume overload, longer hospitalization, more testing, and worsening hyponatremia. 

If overcorrection develops, urgent treatment is required, including discontinuation of 3% sodium chloride, infusion of a 5% solution of dextrose in water, and administration of desmopressin as rescue therapy. Because potassium retention increases serum sodium, special caution is required with potassium supplementation when treating hyponatremia to avoid overcorrection.

Nonemergency Treatment 

Fewer than 5% of patients with hyponatremia have sufficiently severe symptoms to need emergency treatment. For the majority of patients, treatment focuses on addressing the underlying cause (or causes) and is typically administered on an outpatient basis; exceptions include treatment of patients who are hospitalized for management of an underlying cause of hyponatremia or whose serum sodium level is less than 120 mmol per liter. Among patients in the latter group, the absence of severe manifestations is evidence of substantial brain-volume adaptation, so close monitoring of serum sodium levels is indicated during treatment to minimize the risk of osmotic demyelination. If the underlying cause can be reversed (e.g., drug effects or pneumonia), hyponatremia resolves within several days. 

Observational studies in patients with moderate or severe chronic SIAD have shown associations between correction of sodium levels and improvements in neurocognitive performance, motor function, and mood; however, other aspects of patient care, including treatment of associated coexisting conditions, may confound these findings. Limited data from randomized, controlled trials bear out findings of improvement on the physical component score of the 12-item Short-Form Health Survey Questionnaire (a tool for evaluating quality of life) with increases in sodium levels. In addition, increases in serum sodium levels in patients with chronic
SIAD and mild or moderate hyponatremia have been associated with increases in markers of osteoblast function,\textsuperscript{40,41} although the effects on the incidence of fractures are not known. These observations support reasonable efforts to correct hyponatremia of any level in patients with SIAD.

Several therapies are available for patients with SIAD (Table 2). Fluid restriction, the first-line treatment, is inexpensive and safe but of limited efficacy; urine output of less than 1.5 liters per day or urine osmolality greater than 500 mOsm per kilogram of water predicts SIAD that is unresponsive to this approach.\textsuperscript{2,46} A randomized, controlled trial that assessed fluid restriction (fluid intake limited to 1 liter per day) as compared with no hyponatremia treatment in 46 patients with chronic SIAD (in whom transient and reversible causes were ruled out) showed a modest rise in serum sodium levels with fluid restriction (3 mmol per liter vs. 1 mmol per liter at day 4; and 4 mmol per liter vs. 1 mmol per liter at day 30). Only 17% and 4% of patients, respectively, had a rise in serum sodium of at least 5 mmol per liter at day 4.\textsuperscript{42}

Other therapies involve increasing salt, urea, or protein intake,\textsuperscript{16,17,24,26} although data are lacking from randomized, blinded trials. In a retrospective study involving 83 patients with chronic SIAD, patients who took salt tablets (median dose, 5 g per day) had a mean increase in serum sodium levels of 5.2 mmol per liter, as compared with 3.1 mmol per liter in patients who did not receive salt tablets.\textsuperscript{43} Salt tablets plus furosemide are widely used on the premise that replacement of salt lost in the urine promotes aquaresis, thus raising serum sodium levels. However, in an open-label, randomized, controlled trial involving 92 patients with SIAD, treatment with salt tablets plus furosemide and severe fluid restriction as compared with fluid restriction alone resulted in modestly higher sodium levels at day 7 but no difference at day 28; the addition of salt plus furosemide also increased the risk of acute kidney injury and hypokalemia.\textsuperscript{44}

Small observational studies ranging in duration from 2 days to 1 year have shown improvements in sodium levels among outpatients and inpatients who received urea in addition to moderate fluid restriction (fluid intake limited to 1 to 1.5 liters per day).\textsuperscript{24,45} A retrospective study showed that among 12 patients treated only with urea, serum sodium levels increased by 6 mmol per liter over 4 days without incidents of overcorrection or other serious adverse effects.\textsuperscript{46} Urea has been used effectively in managing nephrogenic SIAD.\textsuperscript{45} Patients with SIAD commonly have low protein intake;\textsuperscript{47} increasing protein intake (to approximately 1 g per kilogram of body weight) may ameliorate hyponatremia by mimicking urea therapy, but data regarding this effect are lacking.

Tolvaptan, which competitively inhibits the vasopressin 2 receptor in the collecting duct, is a highly effective therapeutic agent.\textsuperscript{47} In a subset analysis involving 110 patients with SIAD who were included in two randomized, placebo-controlled trials of tolvaptan for the treatment of hyponatremia, patients who received tolvaptan had larger increases in serum sodium levels than patients who received placebo. The average daily area under the curve for the serum sodium level among patients who received tolvaptan was 5.3 mmol per liter from baseline to day 4 and 8.1 mmol per liter from baseline to day 30; among patients who received placebo, the average daily area under the curve for the serum sodium level was 0.5 mmol per liter from baseline to day 4 and 1.9 mmol per liter from baseline to day 30. Patients who received tolvaptan had less need for fluid restriction and a shorter duration of hospitalization than those who received placebo.\textsuperscript{39} However, thirst and dry mouth were common, and overcorrection of hyponatremia occurred in 5.9% of patients treated with tolvaptan.\textsuperscript{39} In an open-label extension of these trials, daily therapy with tolvaptan continued to be effective over 4 years.\textsuperscript{48} Tolvaptan is contraindicated with concomitant use of hypertonic saline, and caution is recommended in patients with serum sodium levels of less than 120 mmol per liter because of limited safety information.\textsuperscript{24,26,47} Tolvaptan is ineffective in the management of nephrogenic SIAD.\textsuperscript{7} A treatment algorithm for SIAD is shown in Figure 2.

More recent data support a potential role for empagliflozin, a sodium glucose cotransporter 2 inhibitor that promotes osmotic diuresis by means of glucosuria, in the treatment of patients with SIAD. In a randomized, controlled trial involving 87 patients, fluid restriction to 1 liter per day plus treatment with empagliflozin was associated with a greater increase in serum sodium levels at day 5 than fluid restriction alone (10 mmol per liter vs. 7 mmol per liter). How-
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Amount or Dose</th>
<th>Efficacy</th>
<th>Adverse Effects</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Fluid restriction</td>
<td>Reduces electrolyte-free water intake and total body water; should include all fluids, not just water</td>
<td>Moderate, &lt;1.5 liters per day; severe, &lt;1 liter per day</td>
<td>First-line treatment; difficult to adhere to and thus often ineffective</td>
<td>Increases thirst; may result in low caloric intake</td>
<td>Inexpensive and safe; predictors of failure at baseline include urine output of &lt;1.5 liters per day, urine osmolality &gt;500 mOsm per kg of water, and the sum of urine sodium and urine potassium levels exceeding the serum sodium level; contraindicated in subarachnoid hemorrhage and other intracranial processes</td>
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<td>Sodium chloride supplement</td>
<td>Increases body sodium content, reduces electrolyte-free water intake, and increases water excretion</td>
<td>2–5 g per day (500 mg per tablet); frequently combined with furosemide 20 mg twice daily or equivalent loop diuretic to increase aquaresis</td>
<td>Limited long-term efficacy</td>
<td>Increases body sodium content, risking sodium and fluid excess; combining with furosemide can cause potassium depletion</td>
<td>Inexpensive; addition of sodium chloride plus furosemide to severe fluid restriction has no persistent benefit with respect to correction of serum sodium levels; contraindicated in hypertension, heart failure, and other sodium-retentive states</td>
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<td>Urea</td>
<td>Increases electrolyte-free water excretion (by means of osmotic diuresis); decreases sodium excretion</td>
<td>15–60 g per day orally or enterally combined with moderate fluid restriction; 30 g of urea (500 mOsm) increases water excretion by 1 liter (for urine osmolality of 500 mOsm per kg of water)</td>
<td>Short- and long-term efficacy reported in observational studies</td>
<td>Nausea, diarrhea, and bitter taste; rare overly rapid correction of serum sodium, but osmotic demyelination not reported</td>
<td>Palatability is improved by dissolving in fruit juice or syrup (European guideline provides a recipe); citrus-flavored U.S. formulation (ure-Na) is available; initially used in Europe but more recently prescribed worldwide; contraindicated in volume depletion, kidney failure, and liver failure</td>
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<td>Tolvaptan</td>
<td>Sole therapy that addresses underlying pathophysiology; competitive vasopressin receptor 2 blocker</td>
<td>15–60 mg per day orally combined with moderate fluid restriction; initiated in hospital to allow close monitoring of serum sodium (every 6–8 hr or more frequently depending on risk of osmotic demyelination syndrome) and dose adjustment; fluid restriction should not be used during the initial dose-finding phase to decrease risk of overly rapid correction of serum sodium; 7.5 mg per day appears as effective as 15 mg per day as a starting dose</td>
<td>Highly effective both in short- and long-term use; aquaretic response and increase in serum sodium correlate directly with severity of hyponatremia</td>
<td>Polyuria and increased thirst; overly rapid correction of serum sodium occurs in 13 to 25% of patients in real-life experience (appears to be exclusive to baseline serum sodium of &lt;125 mmol per liter); sporadic cases of osmotic demyelination syndrome; 7.5-mg dose not associated with overly rapid correction in chronic SIAD</td>
<td>Food and Drug Administration warns against use for &gt;30 days (on the basis of duration of pivotal trials) and in patients with liver disease; not recommended by the European guideline owing to risks of overly rapid correction of serum sodium level and hepatotoxicity; hepatotoxicity not observed in tolvaptan trials for hyponatremia, but reversible hepatotoxicity was reported in trials that used high doses of tolvaptan to alter course of polycystic kidney disease; cost is a barrier to use in some countries</td>
</tr>
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Severe symptoms, moderately severe symptoms and high risk for progression, or intracranial disease?

Yes

Correct hyponatremia according to guidelines
3% sodium chloride bolus
Fluid restriction
Consultation with specialist

Hyponatremia corrected
Goal: 4–6 mmol per liter within 1–2 hr
Correction limit
Low risk for ODS:
10 mmol per liter within first 24 hr
18 mmol per liter within first 48 hr
High risk for ODS:
8 mmol per liter during any 24-hr period

Hyponatremia overcorrected (correction limit exceeded)
Discontinue 3% sodium chloride
Administer 5% dextrose in water
Administer parenteral desmopressin

Hyponatremia undercorrected (failure to reach goal)
Reassess whether 3% sodium chloride administered was sufficient according to patient’s serum sodium level at baseline and total body water
Enforce fluid restriction

Reassess need for long-term treatment

Transient SIAD?

Yes

No further treatment

No

Treatment of chronic SIAD

No

Fluid restriction
If taking causative medication, discontinue if safe
Treat underlying condition if one identified

Hyponatremia corrected?

Yes

Sodium chloride tablets + furosemide (this choice should be weighed in the context of potential contraindications — e.g., hypertension, fluid overload, hypokalemia, or prostatism)

Reassess need for long-term treatment

No

Urea or tolvaptan
Choice depends on local availability, experience, cost, and contraindications (contraindications to urea include volume depletion, kidney failure, and liver failure; tolvaptan is contraindicated in patients with liver disease)
Moderate fluid restriction
Reassess need for long-term treatment

No

Hyponatremia corrected?

Yes

No

Reassess need for long-term treatment

Treatment of chronic SIAD

No further treatment
ever, although the frequency of serious adverse events did not differ materially between the empagliflozin and placebo groups in that trial, empagliflozin was associated with transient kidney dysfunction in 4 patients and overcorrection of hyponatremia in 2 patients (as compared with no patients and 1 patient, respectively, in the placebo group).49 In a subsequent randomized 4-week crossover trial involving 14 patients, treatment with empagliflozin resulted in an increase of 4.1 mmol per liter in the serum sodium level, as compared with no increase with placebo.50

Areas of Uncertainty

Whether the observed associations between chronic hyponatremia and adverse outcomes (such as fractures and increased risk of death) are causal remains uncertain, although some evidence supports causal relationships. For example, the experimental induction of chronic SIAD in aged rats resulted in loss of bone density, sarcopenia, cardiomyopathy, and hypogonadism.14,51

Whether reversing hyponatremia results in improved long-term outcomes is also uncertain. A meta-analysis of observational studies showed substantially lower occurrences of in-hospital and postdischarge death among patients whose hyponatremia improved during hospitalization as compared with patients whose hyponatremia did not improve.52 However, the possibility of confounding by coexisting conditions and other aspects of treatment cannot be excluded.

Prospective studies are needed to assess emergency management of hyponatremia with the use of guideline-directed fixed doses of hypertonic saline (administered as an intravenous bolus) as compared with an individualized formulation-based approach. Encouraging reports regarding the efficacy and safety of smaller starting doses of tolvaptan warrant additional investigation.53 Long-term randomized trials are needed to compare treatment with tolvaptan, urea, and empagliflozin (as well as other sodium glucose co-transporter 2 inhibitors) with respect to efficacy outcomes, safety, and costs.

Guidelines

Recommendations from a U.S.–Irish expert panel16 and European guidelines17 regarding the diagnosis and management of hyponatremia, including hyponatremia due to SIAD, have been published previously. Our recommendations align with these guidelines.

Conclusions and Recommendations

The patient who is described in the vignette has hyponatremia consistent with SIAD. To confirm the diagnosis, testing is needed to rule out secondary adrenal insufficiency and severe hypothyroidism. Because he is taking no medications associated with SIAD and no other cause is apparent, we would pursue CT imaging of the chest and head; if imaging is negative, we would consider the case idiopathic. His high urine osmolality level predicts a poor response to fluid restriction as monotherapy. Given the patient’s hypertension and prostatism, we would avoid recommending salt tablets and furosemide. We would instead recommend urea at a dose of 15 g twice daily (delivered as an oral urea formulation) along with fluid restriction to 1500 ml per day, although data from randomized trials are not available to support this approach. Alternatively, we would consider long-term use of tolvaptan at a starting dose of 7.5 mg per day; however, the cost of this therapy may be a barrier for some patients. Sodium levels should be closely monitored during treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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