JAMA Diagnostic Test Interpretation

Evaluating Hyponatremia

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A woman in her 30s presented with gradually worsening abdominal pain and was found to have hyponatremia. A glioma of the optic chiasm was treated 20 years prior with chemotherapy and radiation. Sequelae included chronic headaches, anterior hypopituitarism, and hydrocephalus necessitating a ventriculoperitoneal shunt. Medications included analgesics, cyclobenzaprine, sumatriptan, ondansetron, divalproex sodium, gabapentin, furosemide, somatotropin, potassium chloride, vitamin D, and estrogen. Haloperidol was recently added. Blood pressure was 125/87 mm Hg. Mucosae were moist and jugular venous pressure was not well seen. Her cardiopulmonary and abdominal examinations were normal, peripheral edema was absent, and sensorium was clear. **Table 1** shows initial laboratory data.

HOW DO YOU INTERPRET THESE TEST RESULTS?

A. The patient has hypovolemic hypotonic hyponatremia.

B. The patient has euvolemic hypotonic hyponatremia.

C. The patient has hypervolemic hypertonic hyponatremia.

D. The patient has hypervolemic hypotonic hyponatremia.

Table 1. Laboratory Values

Test	Patient's Value	Reference Range
Plasma		
Sodium, mEq/L	122	136-145
Potassium, mEq/L	4.3	3.4-5.0
Total CO_2, mEq/L	26	21-32
Blood urea nitrogen, mg/dL	7	6-20
Creatinine, mg/dL	0.7	0.60-1.10
Glucose, mg/dL	66	60-99
Osmolality, mOsm/kg	251	285-295
Hemoglobin, g/dL	11.0	12-16
Hematocrit, %	31.8	36.0-46.0
Urine		
Osmolality, mOsm/kg	410	Varies
Sodium, mEq/L	138	Varies
Potassium, mEq/L	21	Varies

SI conversion factors: to convert blood urea nitrogen to mmol/L, multiply by 0.357; creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555.

Answer

B. The patient has euvolemic hypotonic hyponatremia.

Test Characteristics

A low plasma or serum sodium concentration usually indicates an excess of water relative to total body sodium and potassium. Thus, hyponatremia is a measure of water imbalance.[1] Plasma sodium concentration measurements can be unreliable in the presence of severe hyperlipidemia or hyperproteinemia (pseudohyponatremia). When plasma has large amounts of other osmotically active organic solutes (eg, glucose or mannitol), true hyponatremia can occur even if the plasma is hypertonic. Therefore, in the presence of hyponatremia, hypotonicity can be confirmed by measuring plasma osmolality. Assessing the extracellular fluid volume is next undertaken to narrow the differential diagnosis. Finally, urine chemistry values can help identify the etiology and guide management (**Table 2**).

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Failure to excrete excess water generally results from an inability to suppress secretion of arginine vasopressin (antidiuretic hormone, ADH) and/or a decrease in effective arterial blood volume (EABV). Transient vasopressin increases may be triggered by pain, nausea, or the postoperative state. Persistent increases in vasopressin levels occur in the syndrome of inappropriate antidiuretic hormone secretion (SIADH; alternatively, the syndrome of antidiuresis[2]) or with certain medications, commonly fluoxetine or sertraline, carbamazepine, vincristine, or cyclophosphamide.[2] Hypovolemic and hypervolemic disorders (eg, heart failure or cirrhosis) often decrease EABV and increase vasopressin levels.[3] Decreased EABV in these disorders stimulates sodium and water reabsorption along the proximal nephron, reducing delivery to the diluting segment (the thick ascending limb of the Henle loop and the distal convoluted tubule). Normally, sodium chloride reabsorption in the thick ascending limb of the Henle loop and the distal convoluted tubule produces dilute tubular fluid necessary for water excretion. Reduced distal delivery of sodium limits the volume of electrolyte-poor urine that can be generated. Hyponatremia from reduced EABV (ie, hypovolemic or hypervolemic but not euvolemic) is characterized by low urinary sodium concentration (eg, <30 mEq/L),[2] reflecting the increased proximal tubular sodium reabsorption (Table 2). Hypervolemic hyponatremia caused by renal failure is identified by abnormal creatinine.

Table 2. Characteristics of Types of Hyponatremia

	Type of Hyponatremia					
	Pseudohyponatremia	Hypertonic	Hypotonic, Subtype[a]			
			Hypovolemic	Euvolemic		Hypervolemic
Plasma osmolality	Normal	High	Low	Low		Low
Causes	Hyperlipidemia, multiple myeloma	Hyperglycemia, mannitol	Salt loss (gastrointestinal, skin, or urinary, primary adrenal insufficiency, diuretics)	SIADH, secondary adrenal insufficiency, severe hypothyroidism	Primary polydipsia, low solute intake	Liver cirrhosis, heart failure
Physical examination	NA	NA	Tachycardia, hypotension, dry mucous membranes	Euvolemia on physical examination		Edema, signs of underlying disease
Urine osmolality, mOsm/kg	>100	>100	>100	>100	<100	>100
Urine sodium, mEq/L	≥30	≥30	<30	≥30	Varies	<30

Abbreviations: NA, not applicable; SIADH, syndrome of inappropriate antidiuretic hormone.

[a] When the blood urea nitrogen concentration is elevated, hypotonic hyponatremia can occur despite normal or elevated measured osmolality. In this case, effective osmolality should be estimated, as described.[2]

According to 2014 Medicare data,[4] national fee limits for plasma and urine sodium and osmolality testing are each less than $10.

Application of Test Result to This Patient

The low plasma sodium concentration suggested relative water excess, which was confirmed by the low plasma osmolality. Physical examination was consistent with euvolemia because of no primary features establishing hypervolemia, peripheral edema, ascites, or hypovolemia. In euvolemic hyponatremia, the distribution of excess water is shared between the extracellular compartment and the much larger intracellular compartment, so edema is not present. Rarely, massive water intake causes hyponatremia by overwhelming a normal urinary diluting mechanism; this is characterized by maximally dilute urine (eg, urine osmolality <100 mOsmol/kg). In this case, the urine osmolality was not maximally dilute, indicating an inappropriate renal response to the water excess. The absence of a urine sodium level of less than 30 mEq/L corroborated the assessment of euvolemia.[2] Therefore, this patient has euvolemic hypotonic hyponatremia. The etiology is likely SIADH attributable to the haloperidol or a central nervous system lesion.

What Are the Alternative Diagnostic Approaches?

Plasma sodium concentration and osmolality are the only laboratory measures for detecting water excess or deficit. Occasionally, secondary adrenal insufficiency or severe hypothyroidism can produce euvolemic hypotonic hyponatremia, and tests of thyroid and adrenal function can be ordered. Either test might show abnormal results in this individual with known hypopituitarism.

Patient Outcome

Because the patient was minimally symptomatic, she was treated with fluid restriction and haloperidol was discontinued. However, her plasma sodium concentration declined further. When the sum of the urine sodium and potassium is lower than the plasma sodium level, the patient is excreting electrolyte-free water and should improve if fluid intake is 1 L per day or less and urine flow is adequate (>1.5 L/d). If the sum of the urine sodium and potassium exceeds the plasma sodium level, as in this case, hyponatremia may worsen, despite fluid restriction, unless the underlying disorder is corrected.[5] The patient therefore required oral sodium chloride, which resulted in a gradual increase in the plasma sodium concentration.[6]

Clinical Bottom Line

- Hyponatremia is a measure of water imbalance.
- In the presence of hyponatremia, hypotonicity is confirmed by a plasma osmolality value of less than 270 mOsm/kg.
- True (ie, hypotonic) hyponatremia usually results from elevated antidiuretic hormone or decreased effective arterial blood volume.
- Hyponatremia due to reduced effective arterial blood volume is characterized by a urinary sodium concentration <30 mEq/L.

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