Water, Water Everywhere…
Diagnosis and Treatment of Hyponatremia

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Why does it matter?

Hyponatremia is defined as a serum sodium concentration below 135 mmol/L. It represents a state of excess body water relative to sodium in the extracellular space. Hyponatremia is the most common electrolyte disorder encountered in clinical practice. It occurs in 4 to 11% of ambulatory patients, in 18% of nursing home residents, and in 15 to 30% of hospitalized patients.[1] Even mild hyponatremia is associated with increased morbidity and mortality. In one prospective study, hospitalized patients with mild hyponatremia of 130 to 134 mmol/L had an increased risk of death (adjusted odds ratio 1.37, 95% confidence interval: 1.23 to 1.52).[2] In another study, asymptomatic chronic hyponatremia was associated with a significant increase in falls, regardless of the sodium level (adjusted odds ratio 67, 95% confidence interval: 7.5 to 607).[3]

Nora's Case

A 76-year-old woman is brought to your office by a family member with a two-week history of generalized weakness, mild confusion, and falls. Her past medical history includes diabetes, hypertension, and depression. She is on metformin 1 g b.i.d., amlodipine 10 mg daily, and escitalopram 10 mg daily. On exam, blood pressure is 140/80 and heart rate is 70 beats per minute with no orthostatic changes. The patient is alert with no neurologic findings. The rest of her exam is unremarkable. Investigations reveal serum sodium 130 mmol/L, potassium 3.5 mmol/L, creatinine 52 mmol/L, serum osmolality 270 mOsm/kg, urine osmolality 310 mOsm/kg, urine sodium 45 mmol/L. What is the next step?

Approach to diagnosis

1. Is it true?

   The first step is to confirm true hypo-osmolar hyponatremia by measuring serum osmolality, which should be low (< 275 mOsm/kg) in patients with hypo-osmolar hyponatremia. Isotonic or hypertonic hyponatremia can occur with hyperglycemia, mannitol therapy, or contrast dye administration. In pseudohyponatremia, there is excess protein or lipid in the blood. These substances stay in the extracellular space and draw water out of cells to cause hyponatremia without any risk of cerebral edema.

Table 1: Causes of Hyponatremia by Extracellular Fluid (ECF) Volume

ECF Volume Status			
Hypervolemic	Euvolemic	Hypovolemic	
		Renal loss (Urine sodium > 30)	Extra-renal loss (Urine sodium < 30)
• Congestive heart failure • Nephrotic syndrome • Renal failure • Cirrhosis	• SIADH • Glucocorticoid deficiency • Hypothyroidism • Low protein diet	• Diuretics • Mineralocorticoid deficiency • Cerebral salt wasting	• Vomiting • Diarrhea • Pancreatitis • Burns • Excessive sweating

Table 2: Causes of the Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Malignancies	Pulmonary Disease	Drugs
Small cell lung cancer	Pneumonia	Desmopressin
Mesothelioma	Asthma	Opioids
Gastrointestinal malignancies	Tuberculosis	Nicotine
Genitourinary malignancies	COPD	SSRIs
Lymphoma		Tricyclic antidepressants
Sarcoma		Cyclophosphamide
		Methylenedioxy-N-methylamphetamine (ecstasy)
Transient	**CNS Disease**	
Nausea	Meningitis	
Pain	Tumours	
Stress	Subdural hematoma	
	Head trauma	

Table 3: Diagnostic Criteria for SIADH[7]

- Serum osmolality < 275 mOsm/kg
- Urine osmolality >100 mOsm/kg
- Clinical euvolemia
- Urine sodium > 40 mmol/L with normal salt intake
- Exclude hypothyroidism and adrenal insufficiency
- No recent diuretic use

2. Is it severe?

The clinical manifestations of hyponatremia are a result of water movement from a relatively hypo-osmolar extracellular space to the intracellular space. Acute hyponatremia develops within 48 hours and is more likely to cause severe symptoms, including seizures, coma, respiratory arrest, neurogenic pulmonary edema, cerebral edema with brain herniation, and death. Chronic hyponatremia is generally associated with milder symptoms, such as headache, nausea, vomiting, confusion, lethargy, and falls.

3. What is the underlying cause?

A volume assessment by clinical and laboratory means can indicate an underlying cause (see Table 1). Laboratory testing should include urine osmolality and urine sodium. If the urine osmolality is greater than 100 mOsm/kg in a hyponatremic patient, this is inappropriately concentrated. If the urine sodium is less than 30 mmol/L, it indicates true or effective volume depletion. In a patient with thiazide-induced hyponatremia, volume status may be low, but the urine sodium will be high from renal losses. The most frequent cause of hyponatremia is the syndrome of inappropriate antidiuretic hormone (SIADH). The criteria for the diagnosis of SIADH are shown in Table 2. There are several causes of SIADH, including malignancies and neurologic and pulmonary disorders (see Table 3). A careful review of medications is also important to identify a reversible cause of hyponatremia.

Treatment

1. Severe hyponatremia

The treatment of hyponatremia depends on its severity and chronicity. Severe hyponatremia requires urgent treatment with hypertonic saline. The infusion rate is calculated by multiplying the patient's weight in kg by the desired correction rate for sodium in mmol/L/h.[5] The serum sodium should be followed every one to two hours. Hypertonic saline should be stopped when symptoms and signs resolve or when the serum sodium reaches 120 mmol/L. Studies have shown that a 4 to 6 mmol/L rise in sodium is adequate to reverse severe symptoms.[6]

2. Rate of correction

When hyponatremia develops, water moves into brain cells, causing swelling. Within two to three days, the brain adapts by exporting solutes to

reduce swelling. If the sodium is corrected in an overly rapidly manner, water loss from brain cells can cause osmotic demyelination. This risk is increased in elderly women on hydrochlorothiazide, alcoholics, and malnourished patients. Previous guidelines set a limit for the rise in sodium correction at 10 to 12 mmol/L in 24 hours and 18 mmol/L in 48 hours.[5] However, osmotic demyelination has been reported even when following these limits.[7] Therefore, newer recommendations suggest correction by 6 to 8 mmol/L in 24 hours, 12 to 14 mmol/L in 48 hours, and 14 to 16 mmol/L in 72 hours.[6]

3. Chronic hyponatremia

In chronic hyponatremia when symptoms are mild or absent, sodium correction is gradual and depends on volume status. If the patient is hypovolemic, isotonic saline should be given first. If the patient is euvolemic or hypervolemic, fluid restriction to less than 500 ml below the daily urine output is recommended. Medications associated with hyponatremia should be discontinued. If possible, underlying diseases should be treated. Vasopressin receptor antagonists are a new class of medications approved for the treatment of hyponatremia that cause a selective water diuresis. They have been proven to safely and effectively increase serum sodium in patients with euvolemic or hypervolemic hyponatremia. However, they are costly and have not yet been shown to improve outcomes. Moreover, there is little experience with such agents in patients with severe hyponatremia, and 3% saline is still the therapy of choice for these patients.

References

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Nora's Case Continued

True hypo-osmolar hyponatremia is confirmed with a serum osmolality of 270 mOsm/kg. Your clinical assessment is that the patient has mild symptoms and is euvolemic by exam and lab criteria. You rule out hypothyroidism and adrenal insufficiency. You suspect SIADH associated with SSRI use and discontinue the SSRI.

FAQs by GPs

1. **I often have patients with mild hyponatremia of 130 to 134 mmol/L. Should I be concerned?**

   Studies show that even mild hyponatremia is associated with a higher risk of falls, fractures, and mortality. All hyponatremia warrants evaluation and treatment.

2. **My patient had hyponatremia that resolved after the thiazide was stopped. Can I ever use a thiazide again?**

   Patients with prior thiazide-related hyponatremia are susceptible to recurrence even after a single dose. They should not be rechallenged.

Take-home Message

1. Assessment of volume status (clinical exam and urine sodium) can indicate the underlying cause of hyponatremia and guide treatment.
2. Severe hyponatremia is a medical emergency requiring hypertonic saline treatment.
3. Recommended rates of correction to avoid osmotic demyelination are 6 to 8 mmol/L in 24 hours.
4. Vasopressin antagonists are safe and effective to increase serum sodium but have not yet been shown to improve outcomes.

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