

**PETER WIDDESS-WALSH, MB**

Department of Neurology, Cleveland Clinic

VIVEK SABHARWAL, MDDepartment of Anesthesiology and Critical Care;
assistant director, Neurology/Neurosurgery
Intensive Care Unit, Cleveland Clinic**SEVAG DEMIRJIAN, MD**Department of Nephrology and Hypertension,
Cleveland Clinic**MICHAEL DeGEORGIA, MD**Cerebrovascular Center and Department of
Neurological Surgery; director,
Neurology/Neurosurgery Intensive Care Unit,
Cleveland Clinic

Neurologic effects of hyponatremia and its treatment

A 73-YEAR-OLD WOMAN with a history of paroxysmal atrial fibrillation, hypertension, and migraine presents with headache, dysarthria, left hemiparesis, and elevated blood pressure (212/159 mm Hg). She is not taking warfarin (Coumadin) or antiplatelet drugs and has no history of trauma.

On examination, she is lethargic with a right gaze deviation, left facial weakness, profound left hemiparesis, and left-sided global neglect. Computed tomography (CT) of the brain shows a 30-cc right frontotemporal capsular hematoma (FIGURE 1).

She is treated with antihypertensive medications and remains hemodynamically

stable. Her hospital course is complicated by bradycardia-tachycardia syndrome (requiring insertion of a pacemaker), aspiration pneumonia, sepsis, and subsequent pulmonary edema (treated with diuretics). Follow-up CT shows no change in the hematoma, and the patient is transferred to the general medical service.

Twenty-one days after admission, she becomes gradually obtunded over the course of several hours, with vomiting. On examination, her right pupil is dilated and responds poorly to light. In addition, she has mild right-sided weakness and a Babinski response in her right foot.

Hyponatremia can cause brain edema as water shifts into the brain by osmosis

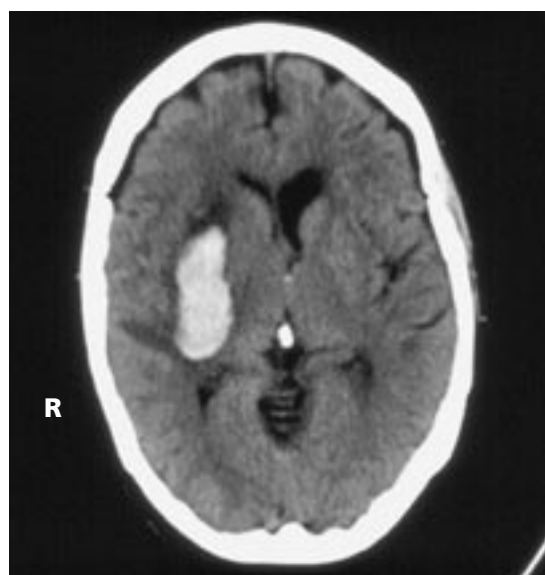


FIGURE 1. Axial computed tomography of the brain without contrast, performed at the time our patient was admitted, shows a right frontotemporal capsular hematoma.

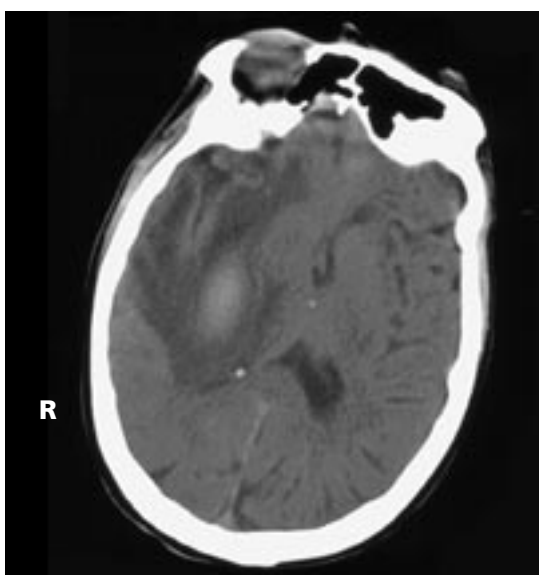


FIGURE 2. Axial computed tomography 21 days after admission shows new cerebral edema and mass effect in the region of the hematoma, but no evidence of recurrent hemorrhage.

TABLE 1

The patient's laboratory values

	PATIENT'S VALUE	NORMAL RANGE
Sodium	121 mmol/L	132–148
Potassium	3.2 mmol/L	3.5–5.0
Chloride	80 mmol/L	98–110
Bicarbonate	33 mmol/L	24–32
Plasma osmolality	260 mOsm/kg H ₂ O	275–295
Urine osmolality	268 mOsm/kg H ₂ O	40–1,400
Urine sodium	76 mmol/L	14–216
Blood urea nitrogen	17 mg/dL	8–25
Glucose	113 mg/dL	65–110
Protein	4.9 mg/dL	6.0–8.4
Total cholesterol	92 mg/dL	100–199
Thyroid-stimulating hormone	2.92 μ U/mL	0.4–5.5
Thyroxine (T4)	6.2 μ g/dL	5.0–11.0
Cortisol (baseline)	15.8 μ g/dL	0.9–26.9
Cortisol (60 minutes after injection of adrenocorticotrophic hormone [ACTH])	19.1 μ g/dL*	

*A normal response is an increase of at least 8 μ g/dL from baseline or an absolute level of at least 18 μ g/dL.

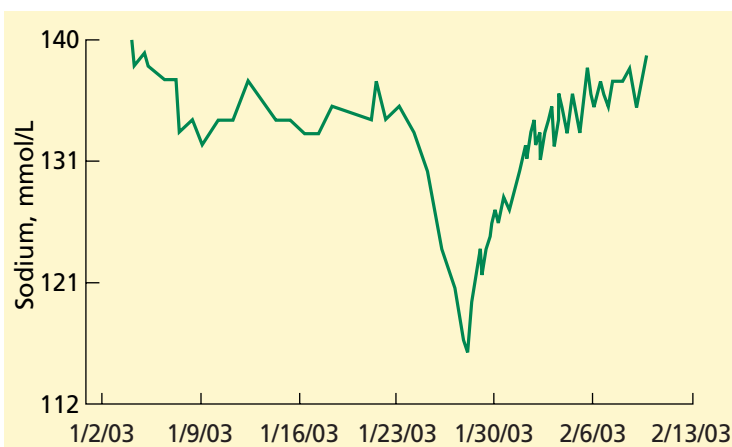


FIGURE 3. Change in serum sodium concentration over time in our patient.

WHICH DIAGNOSTIC TEST?

1 Which test should be ordered next?

- ☐ Repeat CT of the brain
- ☐ Magnetic resonance imaging (MRI) of the brain
- ☐ Electroencephalography
- ☐ Complete blood cell count, biochemistry, and urinalysis

CT should be repeated to detect a new structural lesion or mass effect. In the setting of acute neurologic deterioration, the other studies would involve an unacceptable delay.

A new CT scan is obtained and shows new cerebral edema and mass effect in the region of the hematoma, without evidence of recurrent hemorrhage (FIGURE 2). No structural lesion such as a tumor is seen that would explain the localized edema.

Laboratory tests (TABLE 1) subsequently reveal the cause of the edema: her serum sodium concentration is 121 mmol/L (normal 132–148)—and the next day it reaches a low of 117 (FIGURE 3).

Comment. Hyponatremia can cause brain edema as water shifts into the brain by osmosis from the dilute plasma.¹ Furthermore, it can worsen existing cerebral edema due to other causes such as intracranial mass lesions or hepatic encephalopathy.

POTENTIAL CAUSES OF HYPONATREMIA

Hyponatremia is often iatrogenic, caused by drugs such as thiazide diuretics, oxcarbazepine (Trileptal), selective serotonin reuptake inhibitors, or opiates or due to improper fluid management, eg, giving intravenous hypotonic fluids to patients whose excretion of free water is impaired because of renal dysfunction.

Hyponatremia can also be a result of neurologic diseases such as cerebral hemorrhage, subarachnoid hemorrhage, Guillain-Barré syndrome, head injury, brain tumor, and meningitis.² Two common causes of hyponatremia in neurologic disease are the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting.

SIADH vs cerebral salt wasting

SIADH is diagnosed by the combination of hyponatremia, low serum osmolality, inappropriately concentrated urine (> 100 Osm/kg H_2O), persistently high urinary sodium excretion (> 20 mmol/L), and hypouricemia. Hypoadrenalism and hypothyroidism must be excluded by measuring thyroid function and cortisol levels.

Cerebral salt wasting, recently recognized as a common cause of hyponatremia in patients with neurologic disease, can be misdiagnosed as SIADH. Salt wasting, however, is the primary abnormality. Subsequent volume depletion leads to appropriate ADH secretion (especially if fluid restriction is erroneously undertaken). Natriuretic factors released from the brain in response to injury have been implicated in the pathogenesis.

Comment. To determine the cause of hyponatremia, one should assess the patient's volume status, renal function, plasma and urine osmolalities, and electrolyte concentrations (TABLE 2).¹ It is important to obtain a detailed drug history from the patient, relatives, and other physicians to determine if the patient has been taking any drugs associated with hyponatremia.

Our patient has hypotonic hyponatremia (TABLE 1) due to a loss of solute coupled with a decreased ability to excrete a water load. She does not appear to be dehydrated, and her blood urea nitrogen is normal. Therefore, we conclude that she is more likely to have SIADH caused by her intracerebral hemorrhage, exacerbated by intravenous hypotonic fluids.

■ ELDERLY ARE AT RISK

2 The elderly are more susceptible to hyponatremia and its complications. Why?

- ☐ They are less able to eliminate free water
- ☐ Many of them receive diuretics
- ☐ They have reduced sensation of thirst
- ☐ All of the above

All of the above make the elderly more susceptible to fluid and electrolyte disorders.

Hyponatremia occurs in up to 11% of the hospitalized elderly,³ and is associated with an increased death rate.⁴ Many elderly patients receive thiazide diuretics, and their sensation

TABLE 2

Causes of hyponatremia

Hypovolemic

Acute corticosteroid withdrawal
Cerebral salt wasting
Diuretic use
Gastrointestinal loss
Iatrogenic (insufficient volume, use of hypotonic solutions)
Skin loss

Normovolemic

Adrenal insufficiency
Drug-induced: selective serotonin reuptake inhibitors, oxcarbazepine (Trileptal), opiates, ecstasy, oxytocin (Pitocin)
Hypothyroidism
Iatrogenic (insufficient volume, hypotonic solutions)
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Hypervolemic

Acute renal failure
Cirrhosis
Congestive heart failure
Iatrogenic (insufficient volume, hypotonic solutions)
SIADH

Plasma osmolality normal or increased

Pseudohyponatremia

of thirst is diminished.⁵ They are also less able to excrete a water load in response to a thiazide diuretic, and less able to conserve sodium because they have lower levels of renin and aldosterone. The elderly, especially women, have smaller plasma volumes than younger patients.

Comment. Suspect hyponatremia if an elderly patient presents with a change in mental status, nausea, or seizures, and particularly in an older patient treated with diuretics or with preexisting structural neurologic disease. The aging brain is more susceptible to encephalopathy or seizures from acute medical conditions.

■ ACUTE VS CHRONIC HYPONATREMIA

3 Which most determines the severity of symptoms in hyponatremia?

- ☐ The degree of hyponatremia (ie, the absolute sodium concentration)
- ☐ The age of the patient
- ☐ The rapidity of change in the serum sodium concentration

A rapid fall in serum sodium, as in acute hyponatremia, is more likely to produce clinical symptoms than is chronic hyponatremia.

Acute severe hyponatremia can be defined as a serum sodium concentration below 120 mmol/L within 48 hours.⁶ Symptoms can arise at higher sodium concentrations if the concentration has fallen rapidly. However, the absolute sodium concentration does influence the occurrence of symptoms. In one series,⁷ patients with asymptomatic hyponatremia had a mean serum sodium concentration of 122 mmol/L, compared with 115 mmol/L in patients with symptoms.

If the plasma is dilute, water diffuses into the brain by osmosis. The resulting dilution of the extracellular fluid in the brain causes the brain cells to swell. This is serious, as an increase in brain volume of 8% to 10% can be fatal. Fortunately, a cerebral osmoregulatory mechanism exists, in which brain cells pump out myoinositol, glutamine, glycerophosphorylcholine, betaine, creatine, and taurine,⁸ restoring the osmolality of the cerebral extracellular fluid and limiting the swelling of brain cells.

These adaptive changes take time, so that the rapid changes in serum sodium in acute hyponatremia are more likely to overwhelm this mechanism and cause neurologic symptoms. Hyponatremia that is severe but chronic may be asymptomatic because the brain has had time to adapt. With sustained chronic hyponatremia, the intracellular brain levels of these intermediates become markedly reduced, restoring the cerebral cell volume to normal.⁹

Symptoms of acute hyponatremia

Acute hyponatremia can cause seizures, respiratory arrest, and coma. In a study of critically ill patients, up to one third of cases of otherwise unexplained seizures could be explained by hyponatremia (serum sodium < 125 mmol/L).¹⁰ Symptoms are related to the degree of cerebral edema.¹¹

The onset of symptoms can be explosive, progressing from nausea and headache to generalized tonic-clonic seizures and respiratory arrest within 20 minutes,¹² particularly if the serum sodium concentration is less than 115 mmol/L. Minor symptoms include headache, anorexia, nausea, vomiting, muscle cramps, lethargy, and apathy. Nausea and vomiting may also be early

signs of increased intracranial pressure.

■ CAN HYPONATREMIA CAUSE FOCAL NEUROLOGIC SIGNS?

4 Can a systemic metabolic abnormality cause focal neurologic signs?

- ☐ Yes
- ☐ No

Yes. Hyponatremia typically causes generalized cerebral edema. The edema can be localized to an area of blood-brain-barrier damage, such as intracerebral hemorrhage or stroke.

Focal neurologic signs have also been reported in hyponatremia without a structural lesion and include hemiparesis, monoparesis, ataxia, nystagmus, tremor, rigidity, aphasia, and unilateral corticospinal tract signs.¹¹ Other systemic metabolic abnormalities that can cause focal neurologic signs are nonketotic hyperglycemia and hypoglycemia.

In our patient, in response to the hypo-osmolar state, water was drawn into the site of the hematoma via a breakdown of the blood-brain barrier, causing focal cerebral edema. The edema caused a leftward midline shift of intracranial structures at the level of the peduncles (FIGURE 2). This caused stretching of the ipsilateral oculomotor nerve (causing right pupil dilation) and compression of the contralateral corticospinal tracts (causing right-sided weakness), also called the Kernahan notch phenomenon.

■ TREATMENT OF HYPONATREMIA

5 Which is the appropriate treatment of hyponatremia?

- ☐ Hypertonic saline (3%)
- ☐ Normal saline (0.9%)
- ☐ Fluid restriction
- ☐ Salt tablets

The appropriate treatment of hyponatremia depends on the diagnosis.

In severe acute symptomatic hyponatremia, 3% hypertonic saline is indicated. A maximum increase of 8% to 10% of the initial serum sodium concentration with hypertonic saline is usually adequate in the acute setting.

In chronic symptomatic hyponatremia,

In acute hyponatremia, the onset of symptoms may be explosive

correction can be rapid during the first few hours (to decrease brain edema), followed by a slower correction limited to 10 mmol/L over 24 hours to avoid central myelinolysis. The risk of myelinolysis increases when the serum sodium level is raised by more than 10 to 15 mmol/L/24 hours. In patients with other risk factors for central pontine myelinolysis, such as hypokalemia, liver disease, chronic alcoholism, poor nutrition, hypocorticism, and burns, the rate of correction should not exceed 10 mmol/L/24 hours.¹³

In patients with impaired water secretion due to impaired renal function, there is a role for the use of 1.5% saline with furosemide to induce a hypotonic diuresis and limit extracellular volume expansion.

In SIADH, inducing hypotonic diuresis with saline and furosemide may worsen the hyponatremia. SIADH is treated by removing or treating the underlying cause, and by fluid restriction to approximately 500 mL below the average daily urine values.

In patients with cerebral salt wasting due to brain injury, volume depletion as a result of fluid restriction for presumed SIADH can cause hypotension and brain infarction.¹⁴ Therefore, water restriction should be avoided in patients with hyponatremia due to cerebral salt wasting. Volume repletion with isotonic solutions (eg, 0.9% saline) will improve hyponatremia in cerebral salt wasting by shutting down ADH secretion. This treatment would exacerbate hyponatremia in SIADH patients, who would excrete the sodium and retain the free water.

Correct infusion rates

Hypertonic saline should be given as 3% NaCl at a rate of 1 to 2 mL/kg of body weight/hour. This will increase the serum sodium concentration by 1 to 2 mmol/L/hour (calculation based on no renal excretion). If the patient has severe symptoms (coma, seizures), then a rate of 4 to 5 mL/kg of body weight/hour for 1 to 2 hours is recommended.

The serum sodium must be measured every 1 to 2 hours until the patient is asymptomatic, then every 4 hours, to avoid overcorrection or undercorrection, as variations in urine output may change intended targets. In less severe or diuretic-induced hyponatremia (not SIADH),

TABLE 3

Sodium in intravenous solutions

SOLUTION	SODIUM CONTENT (MEQ/L)
5% dextrose	0
0.45% saline	77
0.9% (normal, isotonic) saline	154
1.5% saline	256
3% saline	513

1 to 2 L of 0.9% saline with potassium can be given over 24 hours. Potassium will also raise serum sodium and osmolality.

To determine the correct rate of infusion, the following formula can be used¹⁵:

$$\text{Change in serum Na} = \frac{\text{Replacement fluid Na} - \text{serum Na}}{\text{TBW} + 1}$$

where the projected change in the patient's serum sodium for 1 L of solution equals the replacement solution sodium concentration (TABLE 3) minus the patient's serum sodium concentration, divided by the total body water (TBW) plus 1. (The total body water can be calculated as the body weight in kilograms multiplied by 0.6 for non-elderly men, by 0.5 for non-elderly women, by 0.5 for elderly men, by 0.45 for elderly women, or by 0.6 for children.) Then divide the desired change in the patient's serum sodium by the projected change in the patient's serum sodium for 1 L of solution (from the formula) to obtain the volume of solution required. The hourly rate of infusion is then determined by dividing the volume of solution by the time (in hours) planned to increase the serum sodium by the desired amount.

■ COMPLICATIONS OF OVERCORRECTION OF HYPONATREMIA

6 Which is the most serious neurologic complication of the treatment of hyponatremia?

- ☐ Lethargy
- ☐ Cerebral edema
- ☐ Seizures
- ☐ Central pontine myelinolysis

0.9% saline helps cerebral salt wasting but worsens hyponatremia caused by SIADH

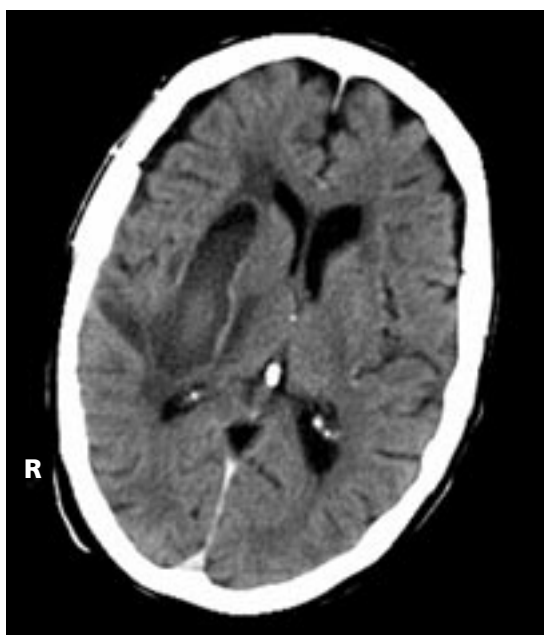


FIGURE 4. After the patient's hyponatremia was corrected, the edema resolved.

In patients with chronic hyponatremia, aggressive correction of hyponatremia can lead to complications, the most serious of which is central pontine myelinolysis.

How central pontine myelinolysis develops

Aggressive treatment of the hypo-osmolar state can reverse the osmotic gradient described above and decrease the effectiveness of brain cell osmoregulation.¹⁶ In an experiment in mice, the brain sodium concentration returned to normal after rapid correction of chronic hyponatremia. However, the levels of brain amino acids and creatine were still reduced by more than a third, causing cerebral dehydration.¹⁷

Acute brain dehydration produced by rapid correction disrupts the tight junctions of the blood-brain barrier.¹⁸ Disruption of the blood-brain barrier results in an influx of activated complement into the brain.¹⁹ Activated complement is toxic to the oligodendrocytes that produce and maintain myelin in the central nervous system.

Correcting acute hyponatremia carries no risk of central pontine myelinolysis, as the changes in brain osmolytes take up to 48 hours to develop.

Central pontine myelinolysis can also

affect extrapontine areas, such as the basal ganglia and other regions of the brain stem, and is then termed extrapontine myelinolysis.

Elderly patients are especially at risk. Elderly patients with diuretic-induced hyponatremia often receive overly aggressive treatment. They are usually minimally volume-depleted, and after the diuretic is stopped, they develop a free water diuresis as their urinary diluting impairment dissipates.²⁰ The hypokalemia that accompanies diuretic-induced hyponatremia is an additional risk factor for central pontine myelinolysis.²¹

Clinical features and diagnosis of central pontine myelinolysis

Clinical symptoms of central pontine myelinolysis typically do not occur until a few days after the rapid correction. The classic presentation is a pseudobulbar palsy and spastic quadriparesis.

In a series of 44 patients, myelinolysis occurred after a mean of 6.3 days (range 3–11) and resulted in a “locked-in” syndrome in 23 patients. Characteristic MRI changes in the pons were seen in 31 patients. In long-term follow-up of 32 survivors of the acute phase of central pontine myelinolysis, 11 had no functional deficit, 11 had minor neurologic deficits, and 10 had severe deficits requiring dependent (ie, long-term) care. Neurologic deficits were static except when myelinolysis occurred in basal ganglia and dystonia developed later.²²

MRI is the definitive test for central pontine myelinolysis, in which T2-weighted images show symmetrical foci of high signal intensity. A negative MRI scan, however, does not exclude central pontine myelinolysis, as the changes can be delayed for 3 to 4 weeks.

Sequelae may be subtle

The sequelae of central pontine myelinolysis may be subtle, consisting of persistent cognitive deficits on neuropsychological testing.²³ The severity of neurologic sequelae does not necessarily follow the improvement in serum sodium values or improvement in appearance on MRI.

Correcting overly aggressive treatment

When patients are overtreated, neurologic damage can be prevented by reducing the

Raising the serum sodium by more than 10 mmol/L/24 hours in chronic hyponatremia increases the risk of myelinolysis

serum sodium concentration back down with hypotonic fluids such as 5% dextrose or oral water, so that the daily increase in serum sodium remains below 10 mmol/L/24 hours. Desmopressin (DDAVP) 4 µg subcutaneously can also be used with hypotonic fluids to reduce the sodium in case of acute overcorrection.²⁴ Dexamethasone was recently reported in animal studies to have a protective effect on osmotic-induced demyelination.²⁵

■ CASE REVISITED

Our patient was treated with fluid restriction, and her serum sodium level returned to normal. Follow-up CT after correction of the hyponatremia revealed resolution of the edema (FIGURE 4). This response supported the diagnosis of SIADH: if she had had cerebral salt wasting, she may have become

hypotensive due to volume depletion, and she would have been at risk for cerebral infarction.

■ KEY POINTS

- Hyponatremia is a common cause of neurologic morbidity in hospitalized patients and is most often iatrogenic.
- Acute hyponatremia may cause cerebral edema due to underlying osmotic interactions between brain cells and the extracellular fluid compartment.
- Rapid correction of chronic hyponatremia may result in myelinolysis and potentially irreversible central nervous system damage.
- The elderly are particularly susceptible to hyponatremia and to complications from its incorrect treatment.

■ REFERENCES

1. Verbalis JG, Martinez AJ. Neurological and neuropathological sequelae of correction of chronic hyponatremia. *Kidney Int* 1991; 39:1274–1282.
2. Rabinstein AA, Wijdicks EFM. Hyponatremia in critically ill neurological patients. *Neurologist* 2003; 9:290–300.
3. Kleinfeld J, Casimer M, Bona S. Hyponatremia as observed in a chronic disease facility. *J Am Geriatr Soc* 1979; 27:156–161.
4. Terzian C, Frye EB, Piotrowski ZH. Admission hyponatremia in the elderly: factors influencing prognosis. *J Gen Intern Med* 1994; 9:89–91.
5. Phillips PA, Rolls BJ, Ledingham JGG, et al. Reduced thirst after water deprivation in healthy elderly men. *N Engl J Med* 1984; 311:753–759.
6. Decaux G, Soupart A. Treatment of symptomatic hyponatremia. *Am J Med Sci* 2003; 326:25–30.
7. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine* 1976; 55:121–129.
8. Trachtman H, del Pizzo R, Sturman JA. Taurine and osmoregulation. III. Taurine deficiency protects against cerebral edema during acute hyponatremia. *Pediatr Res* 1990; 27:85–88.
9. Trachtman H. Cell volume regulation: a review of cerebral adaptive mechanisms and implication for clinical treatment of osmolar disturbances: II. *Pediatr Nephrol* 1992; 6:104–112.
10. Wijdicks EF, Sharbrough FW. New-onset seizures in critically ill patients. *Neurology* 1993; 43:1042–1044.
11. Riggs JE. Neurologic manifestations of electrolyte disturbances. *Neurol Clin* 2002; 20:227–239.
12. Arieff AI. Hyponatremia, convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986; 314:1529–1535.
13. Soupart A, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications. *Clin Nephrol* 1996; 46:149–169.
14. Wijdicks EF, Vermeulen M, Hijdra A, van Gijn J. Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: is fluid restriction harmful? *Ann Neurol* 1985; 17:137–140.
15. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; 342:1581–1589.
16. Boulard G. Osmolarité plasmatique et volume cérébral. *Ann Fr Anesth Réanim* 2001; 20:196–202.
17. Thurston JH, Hauhart RE, Nelson JS. Adaptive decreases in amino acids (taurine in particular), creatine, and electrolytes prevent cerebral edema in chronically hyponatremic mice: rapid correction (experimental model of central pontine myelinolysis) causes dehydration and shrinkage of the brain. *Metab Brain Dis* 1987; 2:223–241.
18. Adler S, Verbalis JG, Williams D. Effect of rapid correction of hyponatremia on the blood brain barrier of rats. *Brain Res* 1995; 679:135–143.
19. Baker EA, Tian Y, Adler S, Verbalis JG. Blood-brain barrier disruption and complement activation in the brain following rapid correction of chronic hyponatremia. *Exp Neurol* 2000; 165:221–230.
20. Verbalis JG. Adaption to acute and chronic hyponatremia: implications for symptomatology, diagnosis and therapy. *Semin Nephrol* 1998; 18:3–19.
21. Lohr JW. Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia. *Am J Med* 1994; 96:408–413.
22. Menger H, Jorg J. Outcome of central pontine and extrapontine myelinolysis. *J Neurol* 1999; 246:700–705.
23. Vermetten E, Rutten SJ, Boon PJ, Hofman PA, Leentjens AF. Neuropsychiatric and neuropsychological manifestations of central pontine myelinolysis. *Gen Hosp Psychiatry* 1999; 21:296–302.
24. Soupart A, Ngasa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. *Clin Nephrol* 1999; 51:383–386.
25. Sugimura Y, Murase T, Takefiji S, et al. Protective effect of dexamethasone on osmotic-induced demyelination in rats. *Exp Neurol* 2005; 192:178–183.

ADDRESS: Peter Widdess-Walsh, MB, The Institute of Neurology and Neurosurgery at St. Barnabas, 101 Old Short Hills Road, Suite 415, West Orange, NJ 07052.