CLINICAL VIGNETTE

Hypernatremia Reviewed: A Case of Hypodipsic Hypernatremia in a Young Woman

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Case Report

A 36-year-old female presented with buckling of her legs and unsteadiness on her feet for 1week. She also reported a 6-month history of generalized weakness and short term forgetfulness, as well as one month of non-localizing lower extremity weakness. Occasionally, she experienced mild, bilateral headaches, but denied falls, postural change, dizziness, vertigo, nausea, vomiting, visual change, numbness, or tingling. Review of systems was negative for cold intolerance, dry skin, weight gain, polyphagia, polyuria, or polydipsia. She was able to drink but, in general, was not thirsty. Her last menstrual period was 2 months prior to presentation, and she had been trying to conceive for 6 months without success.

Her past medical history was significant for hepatocellular cancer (fibrolamellar type) diagnosed 12 years prior to presentation, treated with left hepatic lobe segmental excision. After three and five years, respectively, she developed metastases to the lung and mediastinum, and both lesions were successfully resected. She was then started on celecoxib and managed expectantly with no evidence of disease for the last four years. She took no other prescribed medications, but supplemented her diet with L-arginine and fish oil.

Her family history was notable for breast cancer deaths in her mother and maternal grandmother at ages 44 and 59, respectively.
On examination her blood pressure was 119/64 mmHg without orthostatic changes; resting pulse was 86 bpm, weight 57 kg, and height 158 cm. Physical examination was unremarkable except for slight unsteadiness of tandem gait on neurological exam.

Laboratory data:

Serum chemistries: Na^+ 176 mmol/L, K^+3.6 mmol/L, Cl^- 133 mmol/L, $HCO3^-$ 36 mmol/L, BUN 33 mg/dL (11.8 μmol/L), creatinine 1.0 mg/dL (88.4 μmol/L), glucose 91 mg/dL (5 mmol/L), Ca^{2+} 8.5 mg/dL (2.1 mmol/L), Mg^{2+} 2.1 mg/dL (0.86 mmol/L).
Urine studies: urine specific gravity 1.032, urine electrolytes: Na^+ 199 mmol/L, Cl^- 210 mmol/L, K^+ 71 mmol/L, urine osmolality 1172 mmol/kg, urine gonadotropins: negative.

MRI of the brain (Figure 1) revealed a large heterogeneous mass in the suprasellar cistern and anterior third ventricle measuring 3.0 cm x 4.9 cm, x 3.4 cm, consistent with a craniopharyngioma or germ cell tumor displacing the optic chiasm and pituitary infundibulum.

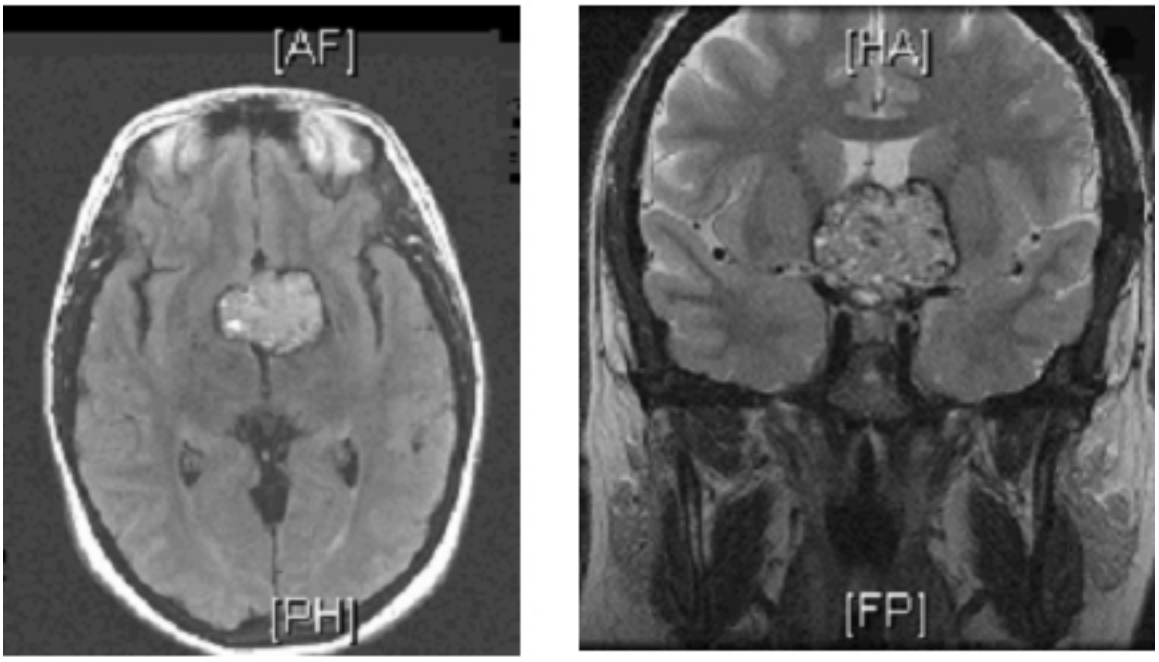

Figure 1. MRI brain. Transverse (left) and frontal (right) views. Large 3.0 cm x 4.9 cm x 3.4 cm heterogeneous mass in the suprasellar cistern, displacing the optic chiasm and pituitary infundibulum.

Hospital Course

The patient was admitted to the intensive care unit. Her calculated serum osmolality was 369 mmol/kg with a free water deficit of 7.3 L. Hydration was started with 0.45% normal saline at a rate of 150 ml/hr, and serum sodium level decreased to 168 mmol/L after 24 hours. On day 3 she began an oral fluid prescription of 2-3 liters of water daily. She was discharged with a serum sodium concentration of 147 mmol/L with the assumption that her new osmotic set point was at a sodium level of approximately 150 mmol/L.

Discussion

Hypernatremia is a common electrolyte disorder defined as an elevation in serum sodium concentration exceeding 145 mmol/L[1]. It is further categorized as acute hypernatremia, developing within 2 days of presentation, or chronic hypernatremia, after 2 days[2] . This distinction is important because the chronicity of the disturbance dictates its appropriate management; furthermore, diagnostic errors in recognizing this difference may result in catastrophic consequences.

Epidemiology

The incidence of hypernatremia varies from less than 1% to over 3%, according to the patient population and the threshold for hypernatremia used in various studies[3]. Mortality rates are high, ranging from 42% to 60%[4]. The variability in these rates is related to the both the severity of the hypernatremia and the rapidity of its onset[1]. However, cautious interpretation of the mortality data is warranted because it is difficult to estimate the relative contributions of the underlying disease and the hypernatremia itself to mortality[4].

Hypernatremia develops in both outpatients and hospitalized patients. Hospital-acquired hypernatremia occurs more commonly and is largely iatrogenic,[1,4] representing 57% of all hypernatremia cases in one study of elderly patients[5]. When present on admission to the ICU, hypernatremia is an independent risk factor for predicting a poor prognosis. If acquired during ICU admission, it has been associated with an increased risk of hospital mortality after adjustment for severity of illness on ICU admission[6-9].

Increasing age is a major independent risk factor for hypernatremia[10]; while hypernatremia that antecedes hospitalization is frequently a geriatric condition, hospital-acquired hypernatremia has an age distribution reflective of the overall hospitalized population[4].

Since sustained hypernatremia exists only in persons with impaired thirst or inaccesibiity to water, those at high risk are infants with diarrhea,[1] and elderly persons with fever, intercurrent illness,[5,11] or defects in thirst related to advancing age[12,13] (geriatric hypodipsia). Other high risk groups include patients with mental status alteration[5] or mental or physical disablility,[11] intubated patients, and nursing home residents who depend on others for hydration[1].

Pathophysiology

Hypernatremia is a disturbance of water balance, resulting in a rise in serum (plasma) sodium concentration[1].

Water comprises 50% of body weight in men and 60% in women, based on gender variations in adiposity. Total body water (TBW) is compartmentalized into the intracellular fluid (55-75%) and the extracellular fluid (25-45%), The ECF is further distributed into the intravascular space (plasma water) and the extravascular space (interstitium) in a ratio of 1:3. The significant difference in solute composition of ECF and ICF is attributable to both intrinsic cell membrane permeability and integral active and passive transport processes. A transcellular gradient is established by the Na^+- ATPase pump such that approximately 90 % of sodium is restricted to the ECF and almost all of the body potassium is intracellular. Hence, total body sodium directly correlates with ECF volume. In addition, because the cell membrane exhibits free permeablilty to water, the osmolality of the ECF approximates that of the ICF, and, clinically, serum osmolality reflects intracellular osmolality[14].

It is important to distinguish between serum osmolality and serum tonicity because, in the regulation of body sodium, hypothalmic osmoreceptors sense variations in serum tonicity, not osmolality[15].

The serum osmolality (plasma osmolality) is a summation of the individual osmolalities of serum solutes calculated by the following equation:

$$\text{Serum Osmolality (mmol/kg)} = 2(\text{Na})\ (\text{mEq/dL}) + \frac{\text{glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}.$$

In comparison, serum tonicity (effective osmolality) is derived from osmotically active solutes, i.e., those that are impermeable to the cell membrane and that induce transmembrane movement of water. Since urea is an ineffective osmole, sodium and glucose are the primary contributors to tonicity[16 (p247)]. Hypernatremia always signifies hypertonicity of all fluid compartments because an initial rise in ECF tonicity is offset by passive osmosis leading to cell dehydration and intracellular hypertonicity[1].

The brain responds to hypernatremia and consequent cellular shrinkage through osmotic adapation[14,16(p717)] in order to restore the diminished brain volume that develops within minutes of hypertonicity. Partial recovery of brain volume is achieved within hours[1] from transcellular shifts in sodium and potassium (rapid adaptation)[14,17]. Within several days, the brain cell accumulates organic osmolytes (primarily myoinositol, glutamine, and glutamate)[18] through membrane transport and intracellular synthesis (slow adaption)[19]. Thus, in chronic hypernatemia, cell volume is defended by the perpetuation of intracellular hyperosmolarity[18].

Regulation of Serum Osmolality
Normal serum osmolality is 275-290 mmol/kg and is maintained within a tight range by osmoreceptors in the anterolateral hypothalamus able to sense a 1-2% change in serum tonicity[14,20]. These osmoreceptors effect changes in water intake through 1) the release of arginine vasopressin and 2) the stimulation of thirst[16(pp174-5)].

Arginine Vasopressin
Arginine vasopressin (AVP), the human form of antidiuretic hormone, is a nonapeptide synthesized in the magnocellular neurons of supraoptic and paraventricular nuclei of the hypothalamus. Neurosecretory granules transport AVP down the axons of the supraoptichypophyseal tract to the posterior pituitary, and from the paraventricular nuclei to the CSF of the third ventricle via portal capillaries of the median eminence[14,20]. These anatomical relationships dictate that a lesion of the posterior pituitary below the median eminence will not result in permanent diabetes indipidus because AVP can still enter the systemic circulation[16(p168)]. Once released, AVP acts on V2 receptors on the basolateral membrane of the principal cells of the collecting duct, and initiates a cyclic AMP mediated cascade that results in insertion of water channels encoded by the aquaporin-2 gene into the luminal membrane of the collecting duct. The previously water impermeable structure can now facilitate passive resorption of water[14,20,21].

AVP is released in response to both *hypertonicity* and *hypovolemia*. The osmotic threshold for AVP secretion is 282-285 mmol/kg, above which AVP rises linearly with plasma osmolality[20]. Hypovolemic stimulation of AVP results from a decrease in effective circulating volume or effective arterial blood volume (EABV), which is the component of the ECF that perfuses the tissues and, thus, is proportional to total body sodium[16(p247)]. However, baroreceptors in the carotid sinus that mediate AVP secretion are only weakly stimulated by small changes in blood volume[14,20,22] (i.e., 5%-10%)[23]. Only when EABV falls significantly enough to reduce arterial pressure will AVP released[14]. As blood volume decreases, AVP rises exponentially, and, at a 20% volume reduction, AVP levels far exceed the threshold for maximal urinary concentration[23,24] In this way, volume regulation attempts to preserve tissue perfusion[25]. However, in the absence of septic shock,[26] AVP does not function as a significant vasopressor[27] because blood pressure is primarily regulated by sodium excretion and systemic vascular resistance via the renin-angiotensin and sympathetic nervous system pathways, the carotid sinus baroreceptors, and atrial natriuretic peptide[16(pp175-7)].

Thirst
The primary stimulus for water ingestion is thirst, which is activated by 1) increased serum tonicity, sensed by anterior hypothalamic osmoreceptors at a threshold similar to or 2-5 mmol/kg higher than that for AVP,[16(p746)28,29] and 2) decreased ECF volume or blood pressure[20]. The precision of this regulatory mechanism ensures that serum osmolality is maintained despite unpredictable sodium and water ingestion. Thus, patients with diabetes insipidus who excrete large volumes of urine (10-15 L/day) will exhibit a relatively normal serum osmolality sustained by secondary polydipsia[16(p748)]. Conversely, when serum osmolality rises in the presence of maximal AVP secretion, only when thirst or access to water is disturbed will hypernatremia develop[1].

Causes of Hypernatremia
Hypernatremia is classified into euvolemic, hypovolemic, and hypervolemic types based upon clinical assessment of extracellular volume status[30].

Euvolemic hypernatremia results from pure water loss, which occurs with 1) unreplaced water loss (from *extrarenal* and *renal losses*[31] and *inadequate fluid intake*) and 2) water loss into cells (*transient hypernatremia*).

Extrarenal loss of pure water includes insensible losses from the lung and skin, and *renal loss* occurs with partial or complete neurogenic or nephrogenic diabetes insipidus (AVP deficiency or renal resistance, respectively)[31,32].

Unreplaced water loss resulting from *inadequate fluid intake* occurs in patients with primary or secondary hypodipsia, or with restricted access to fluid[1]. Primary hypodipsia is observed with neoplastic, granulomatous, infectious, vascular,[30] or surgical[20,33] lesions that abolish the hypothalmic thirst center, or with osmoreceptor dysfunction causing a decreased sensitivity for osmotically mediated AVP release and a higher osmotic threshold (essential hypernatremia)[34]. In secondary hypodipsia replacement of obligate free water losses is insufficient because of altered mental status, cerebral vascular disease, dementia, or delirium[30]. Debilitating comorbidities or simply reliance on others for hydration may lead to inadequate water ingestion[1] by precluding drinking, rather than thirst.

Transient hypernatremia causes a brief rise in serum sodium of 10 to15 mmol/L, and may be induced by seizure or vigorous exercise as glycogen breakdown increases ICF osmolality, driving water uptake into cells. Resolution occurs within 5-15 minutes of rest[32,34,35]. In all other cases of euvolemic hypernatremia, passive osmosis occurs from the ICF to the ECF in response to rising ECF osmolality, resulting in intracellular dehydration[15]. The fluid deficit in pure water loss is derived from the TBW apportioned as 60% ICF and 40% ECF, of which only 10% is intravascular. While ECF volume is slightly reduced with pure water loss, it is not clinically significant in the absence of a sodium deficit and substantial intravascular volume depletion[1]; consequently, the patient remains euvolemic despite intracellular dehydration[15].

In contrast, *hypovolemic hypernatremia***,** results from combined salt and water deficits and is observed when water loss exceeds that of sodium in the absence of water replacement[36]. Included are *gastrointestinal extrarenal losses* (vomiting, osmotic diarrhea, nasogastric tube drainage, and increased enterostomy output), *cutaneous extrarenal losses* (burns and excessive sweating), and *renal losses* (osmotic and loop diuretics, postobstructive diuresis, and acute tubular necrosis in the polyuric phase)[1,36]. Since sodium is primarily an extracellular solute, ECF volume, and in severe cases, EABV and tissue perfusion are all decreased in hypovolemic hypernatremia; hence, the patient is hypovolemic (from salt and water loss) with coexistent dehydration (from pure water loss).

Hypervolemic hypernatremia is usually iatrogenic and may be precipitated by inappropriate administration of hypertonic solutions,[1] e.g., during resuscitative efforts, dialysis, or hyperalimentation[36]. Other causes include hyperaldosteronism, in which there is an upward resetting of the osmostat for AVP secretion,[32] and Cushing's syndrome[1]. In hypertonic hypernatremia, sodium excess increases ECF volume with a concomitant reduction in ICF volume,[1] resulting in hypervolemia and dehydration.

Clinical Manifestations

An acute rise in plasma sodium occurring over less than 24 hours will eventuate in vascular rupture, cerebral and subarachnoid hemorrhage, permanent neuronal injury, or death, if brain osmotic adaptation does not occur[1,36]. Neurological symptoms correlate with the acuity and severity of the hypernatremia[1] and range from irritability, to weakness, lethargy, hyperreflexia, seizures, coma, and death[3,16(p761)] . The level of consciousness is proportional to the degree of hypernatremia[5,6].

In chronic hypernatremia, cerebral adaptation precludes the development of severe neurologic sequelae[1,17]. Non-neurological symptoms may include adipsia or intense thirst, which diminishes with progressive hypernatremia[1]. Poor skin turgor, dry mucous membranes, orthostatic hypotension, and resting tachycardia reflect hypovolemia, and elevated jugular venous pressure and edema indicate volume overload. Geriatric patients, however, may exhibit minimal symptoms until sodium concentration exceeds 160 mmol/L[5]. As levels exceed 180 mmol/L, mortality rate becomes high[37].

Diagnosis

Once a sodium level greater than 145 mmol/L is confirmed, the volume status of the patient is assessed using details of the history and physical examination including fluid intake, urine output, level of thirst, and orthostatic hypotension. Other laboratory studies should be obtained including: serum electrolytes (K^+, Ca^{2+}), glucose, BUN, creatinine, urine electrolytes (Na^+, $K^{+)}$, urine and serum osmolality, 24-hour urine volume, and plasma AVP level (as indicated).

Use of volume status, urine sodium and urine osmolality provides a simple diagnostic approach to hypernatremia[38,39]. (Figure 2)[1,31-36]

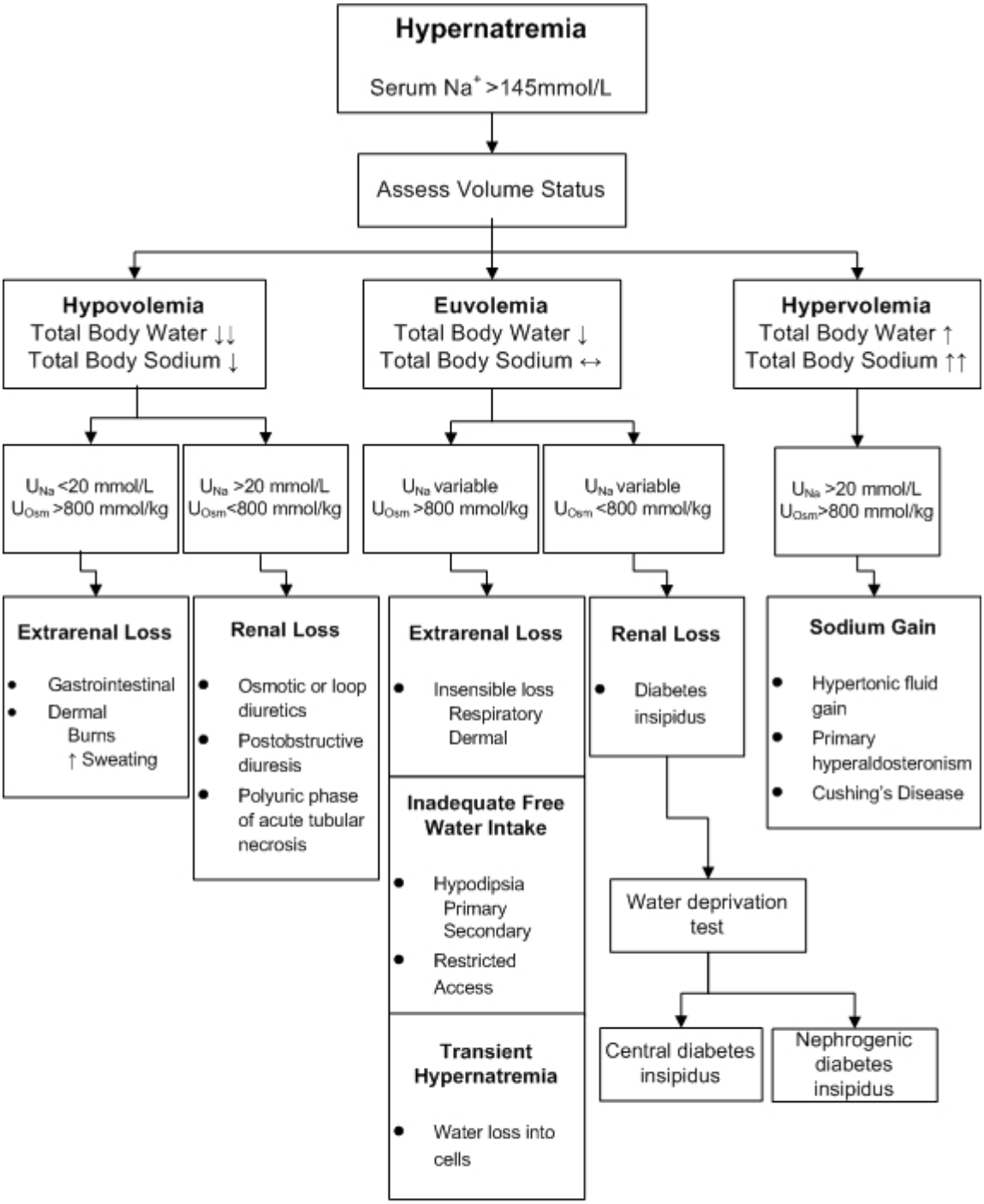

Figure 2. Approach to the diagnosis of hypernatremia.[1, 31-36]
↓ decrease, ↓↓ large decrease, ↑ increase, ↑↑ large increase, ↔ no change
U_{Na}: urine sodium
U_{Osm}: urine osmolality

If *hypovolemia* is established, a urine sodium (U_{Na}) <10-20 mmol/L reflects increased renal resorption of sodium to restore the sodium deficit. In this circumstance, with a urine osmolality (U_{Osm}) >800 mmol/kg, there is extrarenal fluid loss (diarrhea, excessive sweating) with compensatory urinary concentration to

replace the fluid deficit. A urine sodium <20 mmol/L in conjunction with U_{Osm}>800 mmol/kg represents renal etiologies of salt and water loss (osmotic and postobstructive diuresis, and intrinsic renal pathology)[31,38].

In *euvolemia*, U_{Na} varies and may be <20 mmol/L in cases of extrarenal loss (insensible losses), or >20 mmol/L in renal losses (diabetes insipidus). When U_{Osm} exceeds 800 mmol/kg, urinary concentrating ability and AVP secretion are intact, and the patient has primary or secondary hypodipsia, or limited access to water. A urine osmolality <800 mmol/kg, despite hypernatremia, indicates an inability to concentrate the urine, and central or nephrogenic diabetes insipidus (DI) is present[38]. These two entities can be distinguished by the second phase of the water deprivation test. The test is performed by restricting fluid intake then determining the response in urine osmolality and urine volume to the AVP analog desmopressin. In complete central DI there will be a greater than 50% rise in urine osmolality, whereas in complete nephrogenic DI there will be no detectable response. Intermediate elevations in urine osmolality are seen with partial central DI and partial nephrogenic DI. Measurement of plasma AVP can help distinguish between equivocal results[2,16(pp768-72),36].

In *hypervolemic states* the patient is exreting excess sodium and maximally concentrating the urine in response to increased plasma volume and osmolality, respectively,[38] resulting in U_{Na} >20 mmol/L and U_{Osm} >800 mmol/L.

When interpreting osmolality data, it is important to recognize that maximal urine osmolality decreases by 20% in adults 60-79 years of age compared to individuals aged 20-59 years[40].

Treatment
The goals of treating hypernatremia are to 1) correct the volume deficit, 2) normalize serum osmolality, and 3) treat the underlying condition[41].

The water deficit required to reduce to serum sodium to 140 mmol/L is calculated by the equation:

$$\text{Water deficit (L)} = \text{TBW} \times \left(\frac{\text{serum } [Na^+]}{140} - 1\right)$$

Where TBW is premorbid body weight in kg corrected for age and gender. The correction factors are 0.6 and 0.5 for nonelderly men and women, respectively, and 0.5 and 0.4 elderly men and women, respectively[1].

The next step is to determine whether the hypernatremia is acute (<48 hrs) or chronic (>48hrs) because the rate at which fluid can safely be administered is determined by the rate at which the accumulated osmolytes can be extruded from the brain cell[41].

In acute hypernatremia developing over hours (as in accidental sodium loading), rapid correction improves prognosis because accumulated electrolytes are quickly extruded from brain cells[1,11,18]. In these patients, the rate of correction of the serum sodium concentration should not exceed 1 mmol/L per hour. However, rapid correction of chronic hypernatremia leads to rapid water uptake by adapted brain cells (which contain high concentrations of intracellular osmolytes), resulting in cerebral edema. Slow correction allows for equilibration of osmolytes and water, reestablishing normal osmolality without neuronal and glial swelling[11,19]. The maximal rate of correction of serum sodium in chronic hypernatremia should not exceed 0.5 mmol/L per hour and 10-12 mmol/L per day,[1,16(p777)] above which seizures, irreversible neurological injury, or death may ensue[16(p775)].
In general, no more than 50% of the fluid deficit should be replaced within the first 24 hours[31]. Dextrose in water can be used to replace pure water losses, but should be avoided in diabetic patients. Hypotonic

fluids may be administered orally, via nasogastric tube, or intravenously. Isotonic solutions are inappropriate in hypernatremic patients except in cases of hemodynamic compromise[1]. In patients with hypertonic hypernatremia, diuretic therapy is initated to remove the sodium excess followed by water replacement to match urine output[2].

The following formulae[1] are used to calculate the effect of □l L of any intravenous solution on serum Na^+ concentration in mEq/L:

$$\text{Change in serum } Na^+ = \frac{(\text{infusate } Na^+ - \text{serum } Na^+)}{(TBW + 1)}$$

For potassium containing solutions:

$$\text{Change in serum } Na^+ = \frac{(\text{infusate } Na^+ + \text{infusate } K^+) - \text{serum } Na^+)}{(TBW+1)}$$

Using these calculations the infusion volume and rate determined by:

$$\text{Infusion volume (L)} = \frac{\text{Desired change in serum } Na^+ \text{ in 24 hours}}{\text{Expected change in serum } Na^+ \text{ after 1L of infusate}}$$

$$\text{Infusion rate (ml/hr)} = \frac{\text{Infusion volume (L) x 1000}}{24}$$

The calculated infusion rate does not allow for obligatory (13ml/kg)[39] or incidental fluid losses, which should be included in the overall fluid prescription[42]. Serial neurological examinations and serum electrolytes should be performed, initially every 2-3 hours,[2] to guide adjustments in infusion rate.

To prevent recurrent hypernatremia, the underlying disorder must be addressed, e.g., by curtailing ongoing renal and extrarenal water and salt losses, and by prescribing mandatory fluid prescriptions for hypodipsic patients. Central diabetes insipidus is managed with exogenous desmopression (dDAVP) or by paradoxically inducing mild volume depletion using sodium restriction or thiazide diuretics, which decrease polyuria by increasing proximal tubular sodium and water reabsorption. In addition, chlorpropamide and carbemazepine can be used to potentiate the action of AVP, while clofibrate administration will enhance its secretion. NSAIDs are useful in congential nephrogenic DI or lithium toxicity because they augment urinary concentrating ability and lower urine output by inhibiting prostaglandin synthesis[16(pp779-83)].

Case Discussion

The young woman described in this rare case of hypodipsic hypernatremia presented with a slow progression of mild neurological symptoms characteristic of chronic hypernatremia. She was clinically euvolemic although her increased BUN/creatinine ratio (33), suggestive of prerenal azotemia, may be confounded by her use of L-arginine supplementation, which has been shown to increase BUN when catabolized to urea[43]. Her urine osmolality of 1172 mmol/kg reflects maximal urinary concentration indicating intact AVP secretion and action. She exhibited little thirst, and a serum sodium concentration above 150 mmol/L in an alert adult implies an aberrant thirst mechanism,[16(p749)] consistent with the patient's hypothalamic lesion affecting the thirst osmoreceptors. Hypodipsic hypernatremia that impairs thirst will usually correct with water loading; however, after correction of the fluid deficit, the patient's sodium level remained at 147mmol/L, suggesting that there was also injury to the osmoreceptors mediating AVP secretion such that they were now governed by changes in volume (i.e., suppressed by water loading), rather than serum osmolality, as seen in *essential hypernatremia*[32,44,45]. This phenomenon

effectively changes the osmotic threshold for AVP release, but true upward resetting of the osmostat is observed only in mineralcorticoid excess[32].

Essential Concepts in Hypernatremia

Hypernatremia is a disorder of water balance, not sodium balance;[1,16(pp247-9)] and may be euvolemic, hypovolemic, or hypervolemic[30]. Plasma osmolality reflects the serum sodium concentration and is tightly regulated by changes in water uptake and excretion mediated by thirst and AVP release; consequently, sustained hypernatremia can only occur if thirst is impaired, or water is inaccessible[1]. Changes in sodium uptake and excretion regulate plasma volume, but not plasma osmolality, and are modulated by other mechanisms that include the renin-angiotensin and sympathetic nervous systems, the carotid sinus baroreceptors, and atrial natriuretic peptide[16(pp175-7)]. Osmoregulation and volume regulation overlap when AVP and thirst are activated in response to large decreases in plasma volume in an attempt to maintain tissue perfusion.

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