Encephalopathies Caused by Electrolyte Disorders

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ABSTRACT

Some of the most common reasons for metabolic neurologic disturbances in the setting of a general hospital are frequently encountered electrolyte and related osmolality disorders. Hyperosmolality is usually related to hypernatremia and/or hyperglycemia. Identifying the cause and carefully calculating the water deficit is crucial to appropriate management. Hyponatremia may be hypertonic, isotonic, or hypotonic. When hypotonic, it may be hypervolemic, euvolemic, or hypovolemic in nature. Determining the precise nature of the hyponatremia allows the clinician to focus the therapy appropriately. The rate of development of hyponatremia is crucial to safe and appropriate treatment. In acutely developing hyponatremia, hypertonic saline is required, whereas in slowly developing hyponatremia, water restriction and slow correction is required to avoid the syndrome of osmotic demyelination. Disorders of potassium metabolism are also common electrolyte disorders seen in the general hospital. Appropriate diagnosis and management of hyperkalemia and hypokalemia are also discussed.

KEYWORDS: Hyperosmolarity, hypertonicity, hypernatremia, hyponatremia, hypokalemia, hyperkalemia

HYPEROSMOLALITY AND HYPERTONICITY

Normal serum, and therefore body fluid, osmolality is in the range of 275–295 mOsm/kg, but clinically significant deleterious effects are generally seen at levels greater than 325 mOsm/kg. Osmolality may be measured directly by freezing point depression or calculated as serum osmolarity in mOsm/L, using the following formula, which accounts for the millimolar quantities of major serum solutes:

$$2\mathrm{Na}\ (\mathrm{mEq/L}) + \mathrm{glucose}(\mathrm{mg/dL})/18 + \mathrm{BUN}(\mathrm{mg/dL})/2.8$$

Effective hyperosmolality is called hypertonicity and indicates the effect of increased extracellular osmoles to draw water from cells by osmosis. If hyperosmolality is due to hypernatremia, cells will initially shrink until adaptive mechanisms allow cell volume to recover. Similarly, a diabetic with hyperglycemia will lose cell water and develop a hypertonic syndrome. In contrast, azotemia (i.e., an elevated blood urea nitrogen [BUN]) may cause hyperosmolality, but not hypertonicity because the high cellular permeability of urea allows solute movement into cells so that cell water does not leave by osmosis. The difference between hyperglycemia (glucose cannot enter cells) and azotemia is seen by the effect on

the serum Na concentration. Water leaving cells in the hyperglycemic patient lowers serum [Na], while [Na] is not altered by a rise in BUN. Addition of extrinsic osmoles such as mannitol, like glucose, causes hyperosmolality, hypertonicity, loss of cell water, and hyponatremia. On the other hand, alcohols that quickly permeate cells, like ethanol, ethylene glycol, isopropyl alcohol, and methanol act more like azotemia causing hyperosmolality, but not hypertonicity or hyponatremia. Because measured osmolality is increased with addition of these extrinsic solutes, but Na, glucose, and urea are not, there is an osmolal gap defined as the difference between measured and calculated osmolality. The osmolal gap should be < 10 mOsm/L.

Hypernatremia is defined as a serum sodium concentration of greater than 145 mEq/L. In other tissues, hypernatremia leads to loss of intracellular water leading to cell shrinkage. The nervous system is unique in that it is capable of generating (or accumulating from the extracellular fluid) solutes referred to as idiogenic osmoles, such as amino acids (glutamine, taurine, glutamate), polyols (myo-inositol), and methylamines (glycerophosphorylcholine, and choline) to minimize cell shrinkage, a process that is complete in 1 to 2 days. When hypernatremia is unusually severe (serum sodium over 160 mEq/L) these mechanisms fail, leading to encephalopathy. When hypernatremia occurs, antidiuretic hormone (ADH) is released and thirst increases leading to renal retention of ingested water, thereby lowering serum sodium toward normal. Hypernatremia is thus due to a defect in thirst or inability to access water, inadequate release or effect of ADH, loss of hypotonic fluid, or addition of concentrated sodium.

Hyperglycemia is nearly always due to diabetes mellitus caused by inadequate insulin production (type I) or insulin resistance (type II). In neurologic patients, this is often precipitated by stress, infection, or the therapeutic use of glucocorticoids. Azotemia is due to renal failure or inadequate renal perfusion (prerenal azotemia). Hyperosmolar agents, such as mannitol or glycerol, are often used in neurologic patients to treat increased intracranial pressure and may result in hyperosmolality.

Hyperosmolality usually produces a generalized encephalopathy without localizing or lateralizing features, but an underlying focal lesion (e.g., stroke, multiple sclerosis, neoplasm) could become symptomatic under the metabolic stress of a hyperosmolar state. The prognosis of the hyperosmolality itself is good, but the long-term outlook depends upon the cause. For unknown reasons, hyperosmolality alone, particularly when due to hyperglycemia, may lead to continuous partial seizures, even when careful studies fail to uncover any underlying lesion. These seizures generally respond promptly to lowering of the serum glucose.

The treatment of hyperosmolality requires calculation of apparent water losses.

1. Calculate the normal total body water (NTBW) as: Body weight (in kg) × 0.6 = NTBW.
2. Estimate the total body solute (TBS) (sodium + potassium) as: NTBW × 140 mEq/L = TBS. Note that the 140 mEq/L is a normal serum [Na].
3. Calculate the patient's body water (PBW) as follows: TBS/patients serum [Na] = PBW.
4. Calculate the patient's water deficit (PWD) as follows: NTBW − PBW = PWD.
5. Apart from deficit correction, estimate large ongoing losses in the urine (osmotic diuresis or diabetes insipidus) or sweat (fever) and replace.

Replace the water losses so that the serum sodium falls no faster than 2 mEq/L/h using water or 5% dextrose in water (D5W). In the hypotensive or volume-depleted patient, normal saline may first be needed to correct blood pressure. In renal failure patients, dialysis may be required. Insulin is administered, with frequent blood sugar testing, if there is hyperglycemia. Intramuscular and subcutaneous insulin may be unpredictably absorbed, particularly in hypovolemic patients because of poor tissue perfusion. Rapid-acting insulin 0.1 units/kg by rapid intravenous (IV) infusion followed by 0.05 U/kg/h by continuous IV infusion is usually sufficient to reduce the blood sugar adequately and safely, but the mainstay of hyperglycemia correction in the hyperosmolar type II diabetic is volume expansion leading to urinary glucose clearance. Rapid reduction of extreme elevations of glucose should be avoided.

Diabetes insipidus (DI) is recognized as hypernatremia (osm > 292) with simultaneous submaximal concentration of the urine. A subcutaneous dose of vasopressin and a serum ADH level will distinguish central from nephrogenic DI. Treatments include deamino D-arginine vasopressin (DDAVP), an ADH analog used in central diabetes insipidus. Salt restriction and even thiazide diuretics may help in nephrogenic diabetes insipidus.

Hyponatremia

Hyponatremia is defined as a serum sodium less than 135 mEq/L, but may be asymptomatic at levels less than 125 mEq/L in chronic, slowly developing cases. Hypotonicity is always associated with hyponatremia, but hyponatremia may be isotonic (e.g., as an artifact in hyperlipidemia, or hyperproteinemia); hypertonic (e.g., hyperglycemia; mannitol); or hypotonic (impairment of free water excretion in low cardiac output states or the syndrome of inappropriate antidiuretic hormone (SIADH), or with an enormous free water load, as in psychogenic water drinking). Osmolality is estimated using the formula above (see discussion of hyperosmolality) and may be measured in the clinical laboratory. The difference between the calculated and

measured osmolality (the osmolal gap) should not exceed 10 mOsm/L. Factitious hyponatremia is due to a laboratory artifact in diluted samples when the solids of plasma are increased (e.g., hyperlipidemia, severe hyperproteinemia as in myeloma). The undiluted [Na] measured by the blood gas machine and the osmolality are not similarly affected.

The prognosis of hyponatremia depends on the rate and magnitude of the fall in serum sodium and its cause. In acute hyponatremia (a few hours or less), seizures and severe cerebral edema may be rapidly life threatening at serum sodium levels as high as 125 mEq/L, whereas patients may tolerate very low serum sodium levels (even below 110 mEq/L) if the process develops over days or more. Rapid correction of acute hyponatremia may be lifesaving, whereas rapid correction of chronic hyponatremia may be dangerous. Nervous system cells initially swell in hypotonic states, but then compensate for chronic hyponatremia by losing solute to the extracellular space followed by water to restore normal cell volume. If the serum sodium rapidly rises after cells regain normal volume, brain cells can rapidly shrink causing osmotic demyelination (formerly known as central pontine myelinolysis). The clinical picture of osmotic demyelination ranges from mild spasticity to coma, depending on the extent of the demyelinating lesions. The pons is particularly susceptible, possibly simply because the crossing and descending fiber tracts produce a tight grid, which tolerates fluid shifts less well than the rest of the brain. The process, however, is not restricted to the pons and may affect the cerebral white matter as well, leading to the evolution of the name for this disorder from central pontine myelinolysis to pontine and extrapontine myelinolysis to the preferred modern term of osmotic demyelination.

The cause of hypotonic hyponatremia is best determined by dividing all possibilities into three categories based on the clinical estimate of the state of the extracellular fluid space. Blood pressure and heart rate with orthostatic measurements, the central venous pressure (neck vein distention) and the presence or absence of edema, allow all patients with hypotonic hyponatremia to be divided into three types: hypovolemic (reduced effective blood volume with hypotension, tachycardia, and orthostatic intolerance); hypervolemic (edematous states), and isovolemic (retention of free water, no apparent edema).

The diagnosis is made with a measurement of the serum sodium followed by an assessment of extracellular volume. The major diagnoses in each category are hypovolemic hyponatremia (gastrointestinal sodium losses; hemorrhage; renal salt wasting, including the cerebral salt wasting syndrome; diuretic excess; and adrenal insufficiency), hypervolemic hyponatremia (congestive heart failure, hepatic failure with ascites, nephrotic syndrome), and isovolemic hyponatremia

(syndrome of inappropriate secretion of antidiuretic hormone, psychogenic water drinking, hypothyroidism, and resetting of the osmostat). The treatment depends on the type of hyponatremia. In hypertonic hyponatremia, one treats the underlying disorder (e.g., hyperglycemia, exposure to mannitol) and replaces only the estimated salt losses. Factitious hyponatremic disorders (e.g., hyperlipidemia, hyperproteinemia) do not require osmotic treatment; in fact, it may be dangerous to fluid restrict such patients. In hypovolemic hypotonic hyponatremia, volume is replaced with isotonic saline; the underlying renal, adrenal, and gastroenterologic conditions are treated, and the cases of cerebral salt wasting (e.g., intracerebral or subarachnoid hemorrhage) are recognized and treated. In hypervolemic hypotonic hyponatremia, free water restriction is utilized while treating the underlying edematous disorders (e.g., congestive heart failure, liver failure, nephrotic syndrome). In isovolemic hypotonic hyponatremia, one considers the chronicity of the syndrome. In chronic, slowly developing cases of isovolemic hyponatremia, water restriction is utilized. Antagonism of ADH action in SIADH with demeclocycline may be useful if water restriction alone fails. In acute (fewer than 48 hours) rapidly developing isovolemic hyponatremia, 3% saline (containing 513 mEq/L of sodium) is used. This solution contains ~0.5 mEq Na/mL; because total body water is ~50% body weight, then infusions of 3% saline at 1–2 mL/kg will raise the [Na] by 1–2 mEq/L. In an acutely hyponatremic patient, raising the [Na] by 4–6 mEq/L may be of immediate value, but [Na] should not be raised to normal. The correction rate is then slowed to less than 10 mEq/L/24 hours. This is followed by free water restriction. In resistant cases, renal vasopressin receptor antagonists (e.g., conivaptan) may be used.

Some patients with SIADH may become more hyponatremic with saline infusion as the water is retained and the salt excreted. This response can be predicted if the urinary [Na$^+$K] > serum [Na]. In such a case, furosemide may be a useful adjunct to dilute the urine.

Hypokalemia

Hypokalemia is defined as a serum potassium level below 3.5 mEq/L. Serum potassium may be low because of abnormal distribution between intracellular and extracellular potassium or because of excessive potassium losses (renal or extrarenal). Hypokalemia due to excessive cellular potassium uptake may be due to insulin, catecholamines (β2 adrenergic agonists), hypokalemic periodic paralysis, alkalosis, or hypothermia. Extrarenal potassium loss (urine potassium < 20 mEq/d) may be caused by diarrhea (low serum bicarbonate), cathartics, sweating (normal serum bicarbonate), or due to starvation (anorexia). Renal potassium loss (urine potassium more

than 20 mEq/d) may be due to hyperreninemia, hyper-aldosteronism, renal tubular acidosis, diuretic use, and hypomagnesemia. Vomiting, by causing metabolic alka-losis, actually causes renal K losses.

Severe hypokalemia (serum potassium < 3 mEq/L) may be life threatening due to cardiac arrhythmia and severe muscle weakness or paralysis. The diagnosis of hypokalemia is made with a serum potassium meas-urement. Urinary potassium measurement may help determine whether the potassium loss is renal or extrarenal, but it should be borne in mind that such measurements are only valid in the face of normal dietary and urinary sodium, as sodium restriction may result in some masking of renal potassium wastage. The blood pressure and measured serum sodium, bicarbonate, plasma renin level, plasma aldosterone level, and urinary chloride may also help in the differential diagnosis of the cause of hypokalemia. The treatment of hypokalemia depends on the cause. One should correct potassium balance problems, if possible (e.g., reduce β2 adrenergic agonists). Dietary sodium restriction (< 80 mEq/d) will reduce renal potassium losses. Oral KCl is used to supplement high K diets in resistant cases of hypokalemia (30–50 mEq/d). For severe (< 3.0 mEq/L) hypokalemia, especially with cardiac arrhythmias and/or severe muscle weakness, IV KCl may be administered with continuous cardiac monitoring. One should also re-strict K infusions in excess of 20 mEq/h to guard against possible hyperkalemic complications.

Hyperkalemia

Hyperkalemia is defined as a serum potassium concen-tration of > 5.5 mEq/L, but is rarely problematic unless it exceeds 6 mEq/L. Hyperkalemia may be seen in circumstances that cause an excess of whole body potas-sium or not. The causes of hyperkalemia without an excess of potassium are muscle injury (e.g., trauma, persistent seizures, muscle infarction), β2 adrenergic antagonists (e.g., propranolol), insulin resistance, hyper-chloremic metabolic acidosis, digitalis poisoning, depo-larizing muscle relaxants (e.g., succinylcholine), and hyperkalemic periodic paralysis (muscle sodium channel mutation). Common causes of hyperkalemia caused by whole body potassium excess include Addison disease, aldosterone deficiency (e.g., hyporeninemia, angiotensin converting enzyme inhibitor therapy, nonsteroidal anti-inflammatory drugs, heparin), and aldosterone resistance (e.g., renal failure, renal tubular disorders, potassium-sparing diuretics). Pseudohyperkalemia may be seen in states of thrombocytosis, leukemic leukocytosis, or he-molysis in the test tube. A plasma [K] measurement may be helpful to exclude these diagnoses. In addition, poor venous access with a tourniquet causing local tissue ischemia may artifactually raise the [K] level in blood drawn from the affected limb.

The first sign of hyperkalemia is usually peaking of the T wave of the electrocardiogram (ECG), which usually occurs with a potassium level of ∼6.0 mEq/L. As the potassium rises, the QRS complex widens, followed by reduction in its amplitude and then disappearance of the T wave. Heart block and loss of P waves are noted. Sudden cardiac arrest may occur. Muscle weakness usually develops. Hyperkalemia may be suspected when the characteristic electrocardiogram pattern is seen, particularly when combined with weakness, sometimes with paresthesias. The diagnosis is confirmed with measurement of the serum potassium.

If hyperkalemia is considered life threatening because it is producing ECG changes and/or severe muscle weakness, one should treat by protecting the heart against life-threatening arrhythmias, promote redistrib-ution of potassium into cells, and enhance potassium removal. For cardiac protection, one should administer calcium gluconate 10% solution, 20 mL as a rapid IV infusion. To promote redistribution of potassium into cells, one should administer glucose 50 g/hour intra-venously with insulin 5 units by rapid IV infusion every 15 minutes and albuterol 10–20 mg by inhaler. To enhance removal of potassium, one may utilize sodium polystyrene sulfonate (Kayexalate) 15–60 g with sorbi-tol by mouth or 50–100 g by retention enema. Loop diuretics, such as furosemide 40–240 mg intravenously over 30 minutes, are useful in the volume-expanded patient. In severe or resistant cases of whole body potassium excess, and in renal failure, hemodialysis may be utilized.

SUGGESTED READINGS

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