Osmotic Demyelination Unrelated to Hyponatremia

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Osmotic demyelination unrelated to hyponatremia is rarely reported. We present a case of osmotic demyelination in a patient with hypernatremia in the absence of preceding hyponatremia and review previously reported cases of osmotic demyelination in nonhyponatremic patients. We conclude that a rapid increase in serum sodium concentration and plasma tonicity even in the absence of preceding hyponatremia may surpass the brain's capacity for adaptation to hypertonicity and lead to osmotic demyelination in predisposed individuals. Risk factors for osmotic demyelination in patients with chronic hyponatremia and without hyponatremia are probably similar and are usually associated with states of limited brain osmolyte response, such as alcoholism, liver disease (including those undergoing orthotopic liver transplantation), malnutrition, malignancy, pregnancy/postpartum state, severe illness/sepsis, adrenal insufficiency, and metabolic derangements. Clinicians should be vigilant in identifying individuals who may, even in the absence of hyponatremia, have increased susceptibility to osmotic demyelination and avoid rapid fluctuations in serum sodium concentrations in such patients.

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Introduction

Osmotic demyelination, a condition with a variable neuropsychiatric presentation,[1] was first described by Adams et al[2] as demyelination of the basal pons resulting from an osmotic insult. Demyelination can also occur in extrapontine areas involving the basal ganglia, thalamus, gray-white junction of the cerebral and cerebellar cortexes, and lateral geniculate nuclei.[3,4] Pathologic findings include noninflammatory losses of oligodendrocytes and myelin while preserving neurons and axons.[4] Although the most severe form is associated with rapid development of a "locked-in" syndrome marked by quadriplegia and an inability to speak and swallow,[1] many cases are mild or even asymptomatic and may improve with time.[5] Osmotic demyelination is perceived to be primarily a complication of rapid correction of chronic hyponatremia.[6,7]

The precise determinants of osmotic demyelination have still not been fully elucidated. The brain has acute and long-term responses to changes in osmolality.[8] Adaptation to hyponatremia includes rapid extracellular shifting of electrolytes to maintain brain volume. Sodium and chloride ions are lost within minutes and potassium ion loss occurs gradually over several hours.[9] If hyponatremia is sustained, organic osmolytes such as myoinositol, taurine, glutamine, glutamate, creatine, phosphocreatine, and glycerophosphorylcholine are transported into the extracellular space, allowing the brain to maintain cell integrity.[4] When in an already adaptive state, such as chronic hyponatremia, the brain is most vulnerable to osmotic demyelination due to a low intracellular osmolyte level.[1] In response to a hypertonic stress, as in rapid correction, ions reaccumulate swiftly followed by osmotically obligated water. During this process, intracellular sodium and chloride concentrations overshoot normal physiologic concentrations.[4] Compared with the initial intracellular losses, intracellular organic osmolyte reaccumulation is a slower process that can take several days.[9] In this setting, the brain is unable to compensate for the osmotic stress, and cellular dehydration occurs. Blood-brain barrier disruption may occur due to endothelial cell dehydration and shrinkage, leading to impairment of the endothelial tight junctions.[4] It has been shown that blood-brain barrier disruption correlates with osmotic demyelination,[10] perhaps by allowing neurotoxins to injure oligodendrocytes, the cells responsible for myelin production and maintenance. Complement-mediated injury is a likely component of demyelination.[11] Given that grey matter is more vascular and white matter is heavily myelinated, the grey-white matter appositional areas are most susceptible to injury.[12]

In cases of chronic hyponatremia, osmotic demyelination is largely preventable with appropriate correction of sodium concentrations. Much discussion exists on the optimal correction rate. In 1989, Sterns[13] recommended a correction rate not >0.5 mmol/L/h, with a maximum of 12 mmol/L over 24 hours and 25 mmol/L over 48 hours. In

Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

2007, Verbalis et al[14] suggested using lower rates in higher-risk individuals, with a goal of 8 mmol/L in the first 24 hours. In 2012, Adrogué and Madias[6] proposed even lower rates, with 24- and 48-hour maximums of 6 to 8 and 18 mmol/L, respectively, and lower goals in higher-risk patients. Ashrafian and Davey[5] put forward the slowest correction rate of 2 to 3 mmol/L per day. The occurrence of osmotic demyelination despite guideline-directed correction has provided the rationale for recommending even slower rates.

With much of the focus on the management of chronic hyponatremia to prevent osmotic demyelination, the notion that osmotic demyelination can occur in non-hyponatremic patients has largely been ignored. We present a case of osmotic demyelination arising from hypernatremia followed by a review of nonhyponatremic cases of osmotic demyelination.

Case Presentation

Clinical History and Initial Laboratory Data

A 55-year-old man with a medical history significant for type 2 diabetes mellitus, alcoholic cirrhosis, and stage 3 chronic kidney disease was admitted for hepatic encephalopathy and alcohol withdrawal. Management included lactulose enemas every 4 hours and lorazepam as needed. He was also treated for uncontrolled hyperglycemia (blood glucose range, 100-550 mg/dL) with insulin. By hospital day 4, his mentation had improved but not to baseline. Serum sodium concentration on admission was 141 mEq/L.

On the day of consultation (hospital day 4), vital signs revealed a temperature of 37.1°C, heart rate of 94 beats/min, blood pressure of 122/69 mm Hg, respiratory rate of 24 breaths/min, and oxygenation saturation of 98% while breathing ambient air. Intake/output data from the prior 24 hours showed that the patient had voided 14 times and produced 10 stools. Physical examination showed a chronically ill-appearing man who was disoriented but awake and had dry mucous membranes, clear lungs, decreased skin turgor, and hyperactive bowel sounds. Asterixis was not present.

Additional Investigations

Laboratory data on the day of consultation (hospital day 4) are listed in Table 1. Chemistry tests revealed worsening hypernatremia with sodium concentration of 167 mEq/L, with a peak serum sodium concentration increase of 16 mEq/L in 1 day (Fig 1).

Diagnosis

Serum sodium concentration was gradually lowered with hypotonic fluids, as shown in Figure 1. Correction proved difficult due to inaccurate quantification of large volumes of urine (patient refused a urinary catheter) and ongoing gastrointestinal losses. His mentation initially improved with serum sodium concentration correction; however, the encephalopathy worsened without other changes in physical examination findings or serum sodium concentrations. Brain magnetic resonance imaging (Fig 2) revealed hyperintense T2 signal with restricted diffusion within the central pons, sparing peripheral fibers, consistent with osmotic demyelination.

Clinical Follow-up

The very poor prognosis resulting from osmotic demyelination and decompensated cirrhosis led the family to elect hospice care.

Discussion

Osmotic demyelination is usually associated with rapid correction of hyponatremia.[6,7,15] As this case shows, osmotic demyelination can also occur from the development of hypernatremia starting from a normal serum sodium concentration. We reviewed the English-language literature for all adult nonhyponatremic cases of osmotic demyelination syndrome using a MEDLINE search. Because we list only key references in this text, all case reports are tabulated in Item S1. Despite some reports' insufficient electrolyte data or unclear time course of the condition, examination of the complete scope of material allowed us to better assess osmotic demyelination resulting from hypertonic stressors and susceptibility to this entity.

Rapid development of hypernatremia was implicated as the cause of osmotic demyelination in almost a third of the reviewed cases (Item S1). A rapid increase in serum sodium concentration in rats can lead to osmotic demyelination,[16] and a similar derangement starting from hyponatremia or normonatremia seems to lead to osmotic demyelination in humans. Sodium and its anions

Table 1. Laboratory Data on Hospital Day 4

Parameter	Value
Serum	
Sodium, mEq/L	165
Potassium, mEq/L	3.2
Chloride, mEq/L	133
Total carbon dioxide, mEq/L	18
Urea nitrogen, mg/dL	29
Creatinine, mg/dL	2.1
Glucose, mg/dL	265
Phosphorus, mg/dL	3.1
Albumin, g/dL	1.8
Urine	
Specific gravity	1.009
pH	5.0
Glucose	3+
Sediment	Bland
Sodium, mEq/L	69
Potassium, mEq/L	12
Chloride, mEq/L	61
Osmolality, mOsm/L	439