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NEUROCRITICAL CARE SOCIETY

LESSONS LEARNED

Osmotic Demyelination Syndrome Associated with Uremia and Elevated Serum Osmolality

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The Case

A middle-aged man with no known past medical history presented to an outside facility with progressively worsened mental status 1 week after a detached retina repair from an eye injury. At the facility, he had a witnessed cardiac arrest. Return of spontaneous circulation was achieved after 5 min. Given a very swollen and proptotic eye on examination, there was high concern for sepsis from necrotizing fasciitis of the eye and possible meningoencephalitis. He was started on broad spectrum antibiotics and evaluated by an ophthalmologist. The intraocular pressure was normal, but there was concern for emphysema and cellulitis (Fig. 1a). Computed tomography angiogram of the head and neck demonstrated extensive foci of gas in the neck, skull base, bilateral orbits, and venous structures, along with bilateral orbital proptosis with subcutaneous emphysema and large air fluid levels within the right globe (Fig. 1b).

What Other Information Would You Want to Obtain?

In addition to the computed tomography angiogram, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) studies, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), and markers of disseminated intravascular coagulation were obtained at the outside facility. Notably, his D-dimer was > 20 µg/mL and blood cultures were positive for *Streptococcus anginosus* and *Fusobacterium necrophorum*. He had an inflammatory CSF profile with a significant neutrophilic pleocytosis (total nucleated cells > 111 cells/µL), elevated protein (135 mg/dL), and hypoglycorrhachia (45 mg/dL). However, no bacteria or viruses were isolated from CSF. His workup for disseminated intravascular coagulation was negative. He was transferred to our facility after 1 day for further management. Day of hospitalization (DOH) numeration within the following text refers to the stay in our facility. Initial neurological examination demonstrated an erythematous, swollen, proptotic right eye and a grossly normal left eye, poor mental status with the inability to follow commands, intact gag reflex, and spontaneous movement in bilateral upper and lower extremities. There was no obvious neck swelling or crepitus. MRI brain (Fig. 1c, d) and magnetic resonance angiogram head and neck demonstrated right transverse and right internal jugular vein occlusion and punctate bilateral occipital infarcts (not shown).

What Would You Do About the Thrombosis?

Because of venous occlusions on MRI brain and multivascular thrombophlebitis, the patient was started on a heparin drip. Subsequently, his platelets dropped. Given concern for heparin-induced thrombocytopenia, he was transitioned to an argatroban infusion.

Case Continued

During the hospitalization he developed acute tubular necrosis (ATN), attributed to multifactorial etiologies, including septic shock, intravenous contrast, and a significant free water deficit (FWD). Permissive hypernatremia was allowed to treat his cerebral edema. In conjunction with hypernatremia, the patient also had a rapidly rising blood urea nitrogen (BUN) level, which contributed to significant increases in serum osmolality within days.

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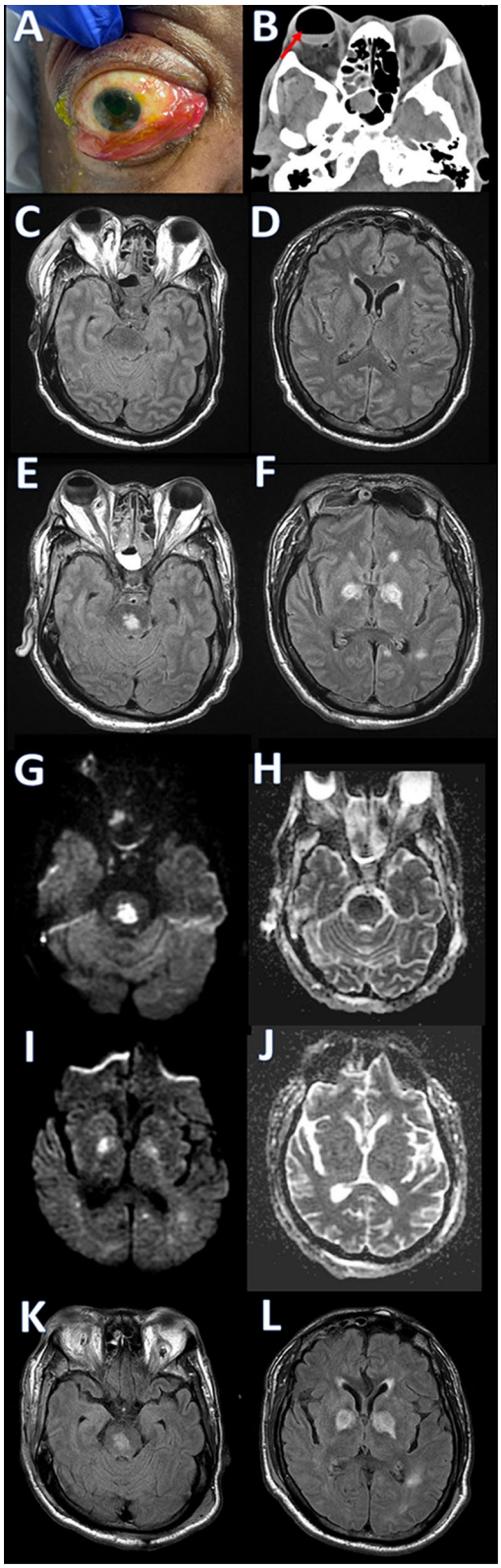

Fig. 1 Examination and imaging. **a** Right eye, concerning for emphysematous and cellulitic process, with gas bubble in the anterior chamber, dilated pupil, and significant proptosis. **b** Large air fluid level (red arrow) within the right globe on CT imaging. **c** and **d** Initial T2 FLAIR on DOH 1 does not demonstrate evidence of extrapontine myelinolysis. **e** and **f** T2 FLAIR and DWI (**g** and **i**) with corresponding ADC (**h** and **j**) on DOH 12 demonstrates FLAIR hyperintensity along the central pons, left periventricular region, and gangliocapsular regions, concerning for sequelae of ODS. There is minimal ADC correlate to diffusion restriction, suggesting T2 shine-through. **k** and **l** Repeat T2 FLAIR on DOH 21 demonstrates evolving signal abnormality along the anatomical regions noted in (**e**, **f**). ADC, apparent diffusion coefficient, CT, computed tomography, DOH, day of hospitalization, FLAIR, fluid-attenuated inversion recovery, DWI, diffusion-weeighted imaging, ODS, osmotic demyelination syndrome (Color figure online)

After multidisciplinary discussion, renal replacement therapy was deferred, and enteral free water supplementation was initiated. Kidney function started improving by DOH 10, and the patient entered the polyuric phase of ATN. During this phase, his hypernatremia significantly worsened (plasma sodium concentration corrected to glucose by the Hillier formula had a peak of 174 mEq/L on DOH 13) due to excessive electrolyte-free urinary water loss, a well-described phenomenon during this phase of ATN. Serum osmolality was calculated using Smithline and Gardner formula [1, 2] ($2 \times \text{sodium} + \text{glucose}/18 + \text{BUN}/2.8$). Measured serum osmolality on DOH 6 was 354 mOsm/kg and calculated serum osmolality was 347 mOsm/kg, indicating that there was no excess osmolar gap (normal osmolar gap < 10 Osm/kg). Given this, calculated serum osmolality was considered a reliable proxy for measured serum osmolality during this hospitalization [1]. At most, his corrected sodium increased by 7 mEq/L twice from DOH 4 to 5 and DOH 9 to 10, and the serum osmolality had the largest increase by 24 mOsm/kg over 24 h on DOH 7 to 8 (Fig. 2).

How Would You Proceed to Correct the Hypernatremia? What Numerical Data/ Laboratories Would You Focus on to Correct it?

The patient had an FWD of 12.2 L (calculated using the patient's gender, weight of 83.9 kg, peak corrected sodium of 174, and desired sodium of 140). Increased enteral free water and continuous dextrose 5% in water infusion were used to replace the FWD and expected ongoing water losses. The patient's corrected serum sodium declined from the peak of 174 to 165 the next day with the ultimate goal of normonatremia. The patient's ATN also resolved, with BUN steadily decreasing from a peak of 191 to 49, without the need for renal replacement therapy.

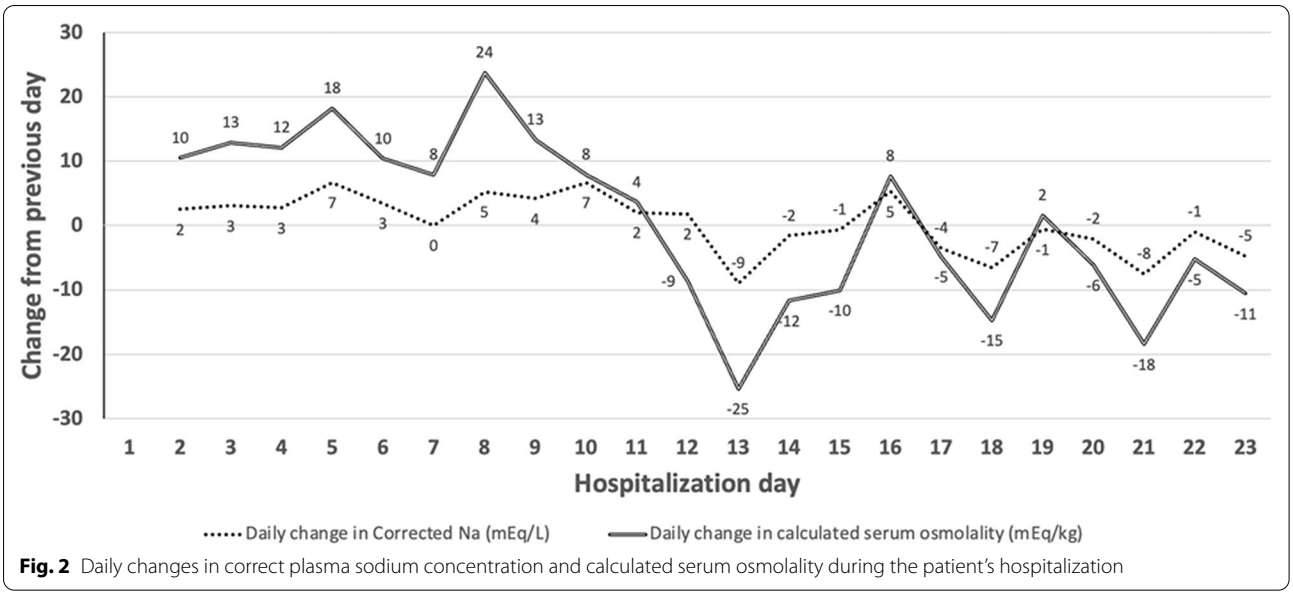

Fig. 2 Daily changes in correct plasma sodium concentration and calculated serum osmolality during the patient's hospitalization

Case Continued

As the FWD was slowly corrected and kidney function recovered, laboratory markers (BUN, creatinine, serum osmolality, and sodium) improved, but the patient remained comatose.

What is the Differential for the Patient's Comatose State After the FWD was Corrected? What Imaging Would You Obtain?

Differential diagnoses included ischemic stroke (due to vasculitis), intracranial hemorrhage, acute hemorrhagic leukoencephalitis (due to intracranial infection), progression of intracranial venous thrombosis, nutritional deficiencies (such as thiamine), uremic encephalopathy, nonconvulsive status epilepticus, and osmotic demyelination syndrome (ODS). Multiple electroencephalograms throughout the hospitalization demonstrated slowing without seizures or epileptiform activity. MRI of the brain and sinuses and magnetic resonance venography was performed on DOH 12 (Fig. 1e–j) and repeated on DOH 21 (Fig. 1k, l). Imaging was significant for multifocal foci of fluid-attenuated inversion recovery hyperintensity along the bilateral gangliocapsular regions and the central pons, concerning for ODS, in addition to extensive persistent intracranial thrombophlebitis (not shown).

What Other Processes Should be Considered with the MRI Findings in Fig. 1?

In a patient with altered mental status, hypernatremia, and kidney dysfunction, these imaging findings are most consistent with ODS. However, without clinical context, they warrant further discussion for other etiologies. Diffusion restriction in the pons can raise concern for acute pontine infarct, although the lack of apparent diffusion coefficient correlate argues against this. Neoplasms, such as lymphoma or gliomas, can demonstrate diffusion restriction and enhancement. Inflammatory demyelinating processes can also present with diffuse fluid-attenuated inversion recovery hyperintensities with varying amounts of diffusion restriction depending on lesion age [3–6]. In a patient with ODS, hallmark signs include the trident sign and piglet sign [5, 7]. These signs may take a week to emerge on imaging and persist for weeks to months [3, 7, 8]. Although our patient did not have these findings on imaging, given the symmetry, especially of the bilateral gangliocapsular regions and clinical context, ODS was felt to be the most unifying diagnosis [3, 5].

What are Common Scenarios in Which Faults are Made by Nephrology or Neurology that May Either Lead to Undercorrection or Overcorrection of Hyponatremia?

Guidelines dictate that hyponatremia should not be corrected more than 8 mEq/L in a 24-h period for high-risk patients, including patients with acute hyponatremia < 105 mEq/L, patients with chronic hyponatremia, patients with alcohol use disorder, patients with malnutrition, patients with hypokalemia (the only risk factor for our patient), and patients with liver disease [9–13]. In less high-risk individuals, rates of 10–12 mEq/L over 24 h may be safe [10]. Despite these guidelines, ODS has been noted in those without rapid correction. A common pitfall is overly slow correction to avoid ODS,

which ultimately is associated with increased length of stay and higher mortality compared with more rapid correction [14]. In one study, the overall in-hospital and 30-day mortality rates for sodium correction of less than 6 mEq/L/24 h were significantly higher than for correction of more than 10 mEq/L/24 h [14].

Discussion

Osmotic demyelination syndrome has been historically reported in cases with rapid correction of hyponatremia and rarely in cases of severe hypernatremia. In 2013, an expert panel recommended a maximum daily sodium correction rate of 8 mEq/L in high-risk hyponatremic patients and 10–12 mEq/L in those not at a high risk [9, 12]. There is controversy surrounding the pace of hyponatremia correction and risk of ODS with recent retrospective studies reporting weak correlation between the two [11, 15]. Macmillan et al. [11] noted that ODS is rare, occurring in 12 of 22,858 hospitalizations for hyponatremia. Of these 12 patients, 7 did not have a sodium correction rate > 8 mEq/L/day [11]. Another large retrospective study of 1024 patients admitted to the intensive care unit with severe hyponatremia noted that rapid correction (> 8 mEq/L/24 h) was associated with lower in-hospital mortality, longer intensive care unit and hospital-free days, and no significant difference in neurological complications [16]. Therefore, it is critical to understand the physiology underpinning transcellular fluid movement across the blood–brain-barrier (BBB) to understand the pathogenesis of ODS.

Acute increases in serum osmolality can trigger osmotic fluid shifts across the BBB, decreasing the volume of neuronal and glial cells [2]. The BBB prevents the passage of sodium. Abrupt increases in serum sodium levels can result in significant adjustments to the volumes of neuronal and glial cells, leading to demyelination and programmed cell death (ODS) [2]. Cells can adapt by uptake of intracellular osmoles to prevent shrinkage, although it is unclear how fast this adaptation can occur. The reflection coefficient, ranging from 0 to 1, is an index of the effectiveness of the solute in generating an osmotic driving force across the neuronal membrane. Sodium has a reflection coefficient of 1.0 across the BBB meaning that it is effectively excluded from diffusing into brain [2, 17].

Urea, possessing a reflection coefficient of about 0.5, only partially traverses the BBB as a solute [2, 17]. As a result, rapid and large increases in serum BUN levels can also contribute to the creation of an osmotic gradient across the BBB, promoting movement of water away from the brain and shrinking the sizes of neurons and glial cells [2, 18]. In our patient, although the elevation in serum sodium levels was gradual and did not exceed daily increments of 8 meq/L, the surge in effective serum osmolality over a few days due to a rapid rise in serum BUN levels resulted in osmotic fluid shifts [19]. This case highlights how both sodium and BUN levels need to be monitored when trying to prevent secondary neurological injury due to osmolality and fluid shifts.

Lessons Learned

1. While targeting permissive hypernatremia, the clinician must also be attentive to overall serum osmolality fluctuations from changes in both serum sodium and BUN levels. Although this patient subsequently had robust kidney recovery, early initiation of renal replacement therapy in this patient would have resulted in the clearance of urea and mitigated the overshoot of serum sodium levels. This may have potentially prevented the development of ODS in our patient.
2. With the wide differential on initial presentation and concern for ocular infection, it is important to acquire intracranial and vessel imaging in addition to serum and CSF studies in an acute neurologic decompensation.

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DK, DLM and MV: literature review, writing, reviewing and revising the manuscript. ASR: literature review, writing, reviewing and revising and oversight of the manuscript.

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