Central Pontine Myelinolysis: The Timing of MRI Finding Is Not Correlated with Clinical Manifestation and Prognosis

Jackson Lin¹, Shih-Jung Cheng², Chih-Jen Wu¹, Han-Hsiang Chen¹, and Yi-Chou Chen¹

¹Division of Nephrology, Department of Internal Medicine
²Department of Neurology, Mackay Memorial Hospital
Taipei, Taiwan, Republic of China

Abstract

Central pontine myelinolysis (CPM) is a dreaded complication from overly rapid correction of hyponatremia. Historically, the prognosis of CPM is dismal. Recent studies showed that improved neurological outcome was possible but reports on improvement in brain imaging are rare. We presented a patient who had not only complete neurologic recovery but also had significant regression on brain magnetic resonance imaging (MRI). In the past, a rise in serum sodium < 12 mEq/L in the first 24 hours was accepted as a safe margin. We now know that an increase in serum sodium concentration by 4-6 mEq/L is enough to overcome the serious neurological complications. When over correction occurs, we could use desmopressin and 5% dextrose solution dextrose solution to lower serum sodium. We should perhaps limit the speed of sodium correction to less than 8 mEq/L in the first 24 hours and allow room for errors. (Acta Nephrologica 2011; 25: 205-208)

KEY WORDS: central pontine myelinolysis, MRI, prognosis, treatment

Case Report

A 67-year-old female with history of hypertension presented with urinary and fecal incontinence for 3 days. She was sent to ER due to progressive weakness and drowsy consciousness. Her serum sodium level was 106 mEq/L and potassium level was 2.0 mEq/L. Initial brain computer tomography (CT) did not show abnormal finding. Hyponatremia was corrected using 3% NaCl and hypokalemia was corrected using normal saline infusion with KCl supplement in the emergency department (ED). Her serum sodium and potassium levels rose to 111 mEq/L and 2.3 mEq/L in 6 hours, respectively. Eighteen hours later, her serum sodium and potassium levels rose further to 118 mEq/L and 2.8 mEq/L in 6 hours, respectively. Eighteen hours later, her serum sodium and potassium levels rose further to 118 mEq/L and 2.8 mEq/L, respectively. She became more alert but appeared agitated. Weakness was much improved. Hypertonic saline was discontinued while she continued to receive normal saline infusion with KCl supplement in the medical ward. Over the next
48 hours, the serum sodium level rose to 128 mEq/L and further to 135 mEq/L in the following 4 days. Her 24-hour urine sodium and chloride concentration collected in the ward on day 3 was 106 mEq/L and 113 mEq/L respectively. The medication history indicated that thiazide used to treat hypertension was the culprit of hyponatremia. After having discontinued the use of thiazide, hyponatremia did not reoccur. Thin elderly females are particularly at risk of developing thiazide-related hyponatremia due to a low total body water content. Hyponatremia usually becomes evident within 14 days of starting thiazide treatment (5). Our patient’s history of progressive weakness and impaired consciousness for days before presentation suggested an insidious onset of hyponatremia. The rest of her hospital stay was uneventful and she was discharged on day 7.

Two weeks later, she was referred to a neurologist due to dysphagia of the fluid, dysarthria and ataxia. Brain MRI showed area of hyperintensity in T2 (Fig. 1a) and hypointensity in T1 images (Fig. 1b) in the pons, which is consistent with central pontine myelinosis. She was able to maintain her daily activities. Over her subsequent visits, her neurological impairment recovered fully. Three years later, brain MRI was performed again for her recently developed memory impairment, which showed encephalomalacia in the pons due to regressions of chronic stage of previous central pontine myelinosis (Fig. 2a, 2b).

**Discussion**

Clinically, hyponatremia is classified as acute or chronic, asymptomatic or symptomatic. Symptomatic hyponatremia is believed to be associated with significant mortality. Brain swelling and hernation might occur in severe hyponatreemic patients (6). In the past, a rise in serum sodium < 12 mEq/L in the first
The rate of IV infusion: Madias formula (8) is often used clinically to determine the rate of IV infusion:

\[
\Delta [\text{Na}_i] = \frac{([\text{Na}^+]_{\text{inf}} - [\text{Na}^+]_{i})}{(\text{total body water} + 1)}, \text{ for 1L of infusate}
\]

Total body water = 0.6 x total body weight in male, 0.5 x total body weight in female. However, we often fail to take into account urinary fluid loss when applying this formula, especially in the emergency setting. Over correction with hypertonic saline due to water diuresis frequently occurs after restoration of volume status and resolution of transit antidiuretic hormone (9). Regrettably, our emergency department failed to record total urine output and check the urine electrolyte. Thus, we cannot demonstrate the rate of correction in serum sodium mathematically. In order to account for the effect of fluid loss (fl) on serum sodium, we could use the reverse formula of Adrogue’-Madias equation (10):

\[
\Delta [\text{Na}_{i}] = ([\text{Na}_{i}^+] - [\text{Na}^+ + K^+]_{i})/(\text{total body water} + 1), \text{ for 1L of fluid (urine) lost}
\]

Selecting appropriate IV fluid to match patient’s serum osmolarity is also important in treating chronic hyponatremia. The osmotic stress in the development of CPM underlines the concept of tonicity balance. In our patient, her calculated serum osmolarity was about 220 mosm/L, both 0.9% saline (310 mosm/L) and 3% saline (1030 mosm/L) were relatively hypertonic. By using 0.33% dextrose/saline 500 mL + 10 meq/L of KCl, which has osmolarity of 240 mosm/L, and oral potassium supplement, we might reduce the risk of CPM in this patient.

Our patient also had hypokalemia, which is regarded as an important risk factor for the pathogenesis of CPM. Patient’s use of thiazide activated the renin-angiotensin system and stimulated the aldosterone secretion, which increased the potassium secretion. Previous studies show that hypokalemia results in decreased concentration of Na-K-ATPase in endothelial cell membrane in the brain, which plays an important role in cell volume regulation (18). Thus, brain cells are more vulnerable to osmotic stress associated with rapid correction of serum sodium. By aggressively correcting hypokalemia first, we might reduce the severity or incidence of CPM in chronic hyponatremic patients.

Fortunately, we now know that an increase in serum sodium concentration by 4-6 meq/L is enough to overcome the serious neurological complication (11). Limited correction in the first few hours followed by slower correction rate and frequent serum sodium monitoring should lower the risk of developing osmotic demyelination while avoiding the dreaded complication of hyponatremia. If the therapeutic limit is exceeded, use of DDAVP and D5W could again lower the serum sodium (12). Some clinicians even suggested administration of DDAVP every 6-8 hours with hypertonic saline for proper correction (13). Several animal models have shown that minocycline has the potential to prevent osmotic demyelination syndrome. Minocycline was administered at the time, several hours before or after the correction of hyponatremia. The incidence and severity of neurological damage were significantly reduced in the study on rats (14). As suggested by Ganken-Kengne et al. (15), minocycline decreased the permeability of the blood-brain barrier mainly by inhibiting microglial activation. Whether minocycline has a role in clinical practice required further studies.

Clinically, patients with CPM often experience a biphasic course. They usually present with encephalopathy secondary to initial hyponatremia, followed by rapid recovery as a normal serum sodium level is restored. The second phase of neurological deteriorations, such as dysarthria, dysphasia or quadriplegia, occurs several days later (16). Our patient had corticobulbar fiber involvement, which resulted in dysarthria and dysphasia. If the corticospinal tract was involved, the patient might have quadriplegia. Previous studies show that in acute phase of CPM clinical deficit may precede the abnormal MRI finding by two to three weeks (17).

Pathologically, CPM is characterized by dissolution of the myelin sheath while sparing the nerve axons. Traditionally, osmotic stress is perceived as the cause of pontine glial cell swelling and apoptosis (19). However, it dose not explain why certain groups of patients are at higher risk of developing CPM. Additional factors might contribute to the demyelination process. Ashrafian and Davey (20) suggested that mitochondrial over-activity during period of insufficient cellular energy might increase production of free radicals, which then contributes to the pro-apoptotic drive. A recent animal study done by Ayus et al. (3) suggested that hypoxia was the cause of brain damage rather than rapid correction of hyponatremia. However, their histological evaluation showed neuronal necrosis in hypoxia-induced lesions, which are different from those of osmotic demyelination (21). Further basic research is needed to truly understand the pathophysiology of the disease process.

MRI is now the modality of choice in diagnosing CPM. It shows a non-inflammatory symmetrical demyelination of the pons. Typical T2-weighted images show a hyperintense lesion in the pons while T1 show hypointense lesion (22). Axial images often show triangular lesion and coronal images often show bat’s wing configuration (23). Improvement in the
appearance of these lesions may be due to resolution of acute edema, remyelination, or decreased astrocytic response (24). Menger and Jörg (25) conducted a study of 44 patients with CPM and found no correlation between the severity of clinical finding and the extent of initial pontine lesion. Clinically, patients might improve despite usually persistent lesions on MRI. Historically, poor prognosis of CPM has been reported (26); however, a more recent study conducted by Menger and Jörg suggested that the majority of patients restored normal health. Our case was unusual in that the patient not only improved neurologically but MRI follow-up 3 years later showed almost complete regression of the lesions.

The best treatment for CPM is to avoid overly rapid correction in the first place. It is important to identify patients with chronic alcoholism, malnutrition or liver disease and perform limited correction of hyponatremia in the first few hours. In addition, there should be room allowed for errors, and variables not usually monitored in the emergency setting, such as water diuresis or half-life of culprit medication, should also be taken into account. In symptomatic hyponatremia, it is better not to have correction exceeding 8 mmol/L in the first day (8). If over correction occurs, DDAVP and/or D5W can be employed to lower again the sodium concentration. Once CPM develops, the treatment is mainly supportive and some patients may eventually recover neurologically. Certain case studies reported that plasmapheresis (27), steroid (28), or thyroid-releasing hormone (29) might be used in treating CPM, but none are conclusive or adopted as standard therapy. Complete neurological recovery following CPM is now possible and we should not give in to the disease easily.

References