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ORIGINAL ARTICLE

Clinical Analysis for Osmotic Demyelination Syndrome in Patients with Chronic Hyponatremia

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Background: Although osmotic demyelination syndrome (ODS) has been well known to be associated with a rapid correction of sodium (Na^+) in patients with chronic hyponatremia, its risk factors and clinical outcomes have not been examined in Taiwan. **Aim:** The aim of the study was to analyze the underlying causes and overlooked risk factors in patients with ODS. **Methods:** We retrospectively collected chronic hyponatremic patients developing ODS and analyzed their clinical characteristics. **Results:** Fourteen patients (7 males and 7 females) with a mean age of 62.7 ± 17.9 years old were enrolled. Their underlying causes included gastrointestinal illness with poor intake (n = 7), chronic use of diuretics (n = 2), syndrome of inappropriate antidiuretic hormone (n = 2), pneumonia (n = 2), and hypopituitarism (n = 1). Their serum Na^+ was 107.2 ± 1.2 mmol/L with mild hypokalemia (potassium 3.1 ± 7 mmol/L), hypoalbuminemia (albumin, 3.4 ± 0.6 g/dL), and hypophosphatemia (phosphorus, 2.3 ± 1.0 mg/dL). Their mean Na^+ correction rate was 8.4 ± 9 mmol/L/day and most patients (60%) developed ODS in first 3 days. Their manifestations included delirium, seizures, unstable gait, aphasia, and drowsy consciousness. Brain magnetic resonance imaging demonstrated that 42.8% had isolated central pontine myelinolysis. Totally, 43% of ODS patients had unfavorable outcome with death and disability. In addition, patients with rapid Na^+ correction rate (>12 mmol/L/day, n = 4) usually exhibited significant hypokalemia (2.5 ± 0.4 vs. 3.5 ± 0.7 mmol/L, $P < 0.05$) as compared with those without. **Conclusion:** Nutritional status and concurrent electrolyte deficiencies such as hypokalemia are major risk factors in patients with ODS. Clinicians should timely recognize these potential risks of ODS and reduce Na^+ correction rate to avoid catastrophic outcomes.

Key words: Hyponatremia, osmotic demyelination syndrome, risk factors, sodium correction rate

INTRODUCTION

Osmotic demyelination syndrome (ODS) characterized by noninflammatory demyelination involving the pons and other areas of the central nervous system is a well-recognized complication following the rapid sodium (Na^+) correction of chronic hyponatremia.[1-5] ODS consists of central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) involving in extrapontine sites.[1,6] The pathogenesis of ODS remains elusive, and the most widely accepted hypothesis is that cellular edema secondary to the fluctuating osmotic forces on the blood-brain barrier leading to compression and subsequent demyelination of fiber tracts and axonal damage.[7-11] The precise incidence of ODS related to chronic hyponatremia remains unclear,[10] but it has been approximately reported from 1% to 11% in hyponatremic patients.[1,12] Once ODS develops, the prognosis is extremely poor with higher mortality.[5] Although ODS is familiar to nephrologists and neurologists, it remains less appreciated to most of general physicians in Internal Medicine and

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Emergency Department because some potential risk factors are easily overlooked.[13,14]

The risk factors for developing ODS are complex, and Na^+ correction rate is the first reported and well discussed in 1986. It recommends that appropriate Na^+ correction rate to avoid neurologic deficit is not exceed 12 mmol/L for 24 h period.[15] However, recent guidelines recommend Na^+ correction rates not exceed 8 mmol/L for 24 h period in the United States guideline[16,17] and not exceed 10 mmol/L in the first 24 h and 8 mmol/L for any 24-h period thereafter in European guideline.[18] Nevertheless, despite enhanced awareness on deceleration of Na^+ correction rate as suggested by textbooks and guidelines, ODS still develops even achieving the limit of Na^+ correction rates. These intriguing relationships suggest that other potentially important risk factors remain to be identified in clinical practice. To the best of our knowledge, there are no case studies of ODS reported in Taiwan.

In this retrospective study, we collected chronic hyponatremic patients with subsequent diagnosis of ODS to analyze the underlying causes, clinical features, laboratory data, radiological finding, risk factors, and the effect of Na^+ correction rate. Results to be reported indicated that 14 patients developed ODS and most of them have gastrointestinal illness with poor intake concomitant with electrolyte imbalance such as hypokalemia and hypophosphatemia. Among patients with rapid Na^+ correction rate, they have significantly hypokalemia compared with those without.

MATERIALS AND METHODS

Study population

The study protocol was approved by the Ethics Committee on Human Studies at Tri-Service General Hospital (TSGHIRB No. 1-105-05-005) in Taiwan. We retrospectively reviewed the medical records from patients with ODS including CPM or/and EPM from January 1, 2001 to December 31, 2011. These diagnostic files of clinical database were electronically interrogated using the ICD-9 diagnostic code 341.8. These cases were confirmed by the clinical presentation with profound hyponatremia (Na^+ <120 mmol/L) or corroborated by classic neuroimaging (brain magnetic resonance imaging [MRI]). Patients who had acute hyponatremia and those with serum glucose 300 mg/dl were excluded. Patients having hypoxia brain injury, neurotoxicity-related demyelination, or infectious condition, younger than 18-year-old, or those with incomplete medical information were also excluded.

Clinical characteristics

Chart abstraction was completed using a standardized data abstraction form. The demographic data including age, gender, body weight, height, initial presentation, underlying causes, and associated comorbidities were analyzed. In addition, initial laboratory tests including serum osmolality, Na^+, potassium (K^+), chloride (Cl^-), total calcium (Ca^{2+}), phosphorus, magnesium (Mg^{2+}), albumin, blood urea nitrogen, creatinine, hemoglobin, bicarbonate ($HCO3^-$), total cholesterol and triglyceride. Urinary biochemistry data were collected. During the management, we also evaluated the clinical course including time to development of ODS, admission to intensive care unit (ICU), mechanical ventilatory support, and clinical outcome. Regarding clinical outcome, these ODS patients who recovered without neurologic deficit were defined to favorable outcome. Disability was defined as inability to perform basic activities of daily living.

Definition of radiologic finding

Brain MRI has been suggested for patients with ODS with neurologic deficit.[19] The radiologic findings of ODS on brain MRI have been defined to be hyperintensity in the central pons and/or various extrapontine structures on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequence and hypointensity on T1-weighted MRI.[20] Lesions restricted to the pons on imaging were classified as CPM, whereas lesions involving sites other than the pons were classified as EPM.

Definition of Na^+ correction rate

The initial serum Na^+ levels and serum Na^+ levels at the 24th h were defined as Na^{+0} and Na^{+24}, respectively. Na^+ correction rate was calculated as ([Na^{+24}-Na^{+0}] mmol/L/day). Rapid Na^+ correction rate was defined as more than 12, 10, 8, and 6 mmol/L/day based on different guidelines.

Statistical analysis

The demographic data and variables were expressed as mean ± standard deviation and percent. The student *t*-test with nonparametric tests were used to compare differences in the clinical laboratory data in patients with ODS between those without rapid Na^+ correction rate and those with. Data analyses were performed using the SPSS program (version 20.0, International Business Machines Corporation, Taipei, Taiwan) and the Prism (v5) software (GraphPad Software). Statistical significance was defined as a $P < 0.05$.

RESULTS

Clinical characteristics

The baseline characteristics were shown in Table 1. Fourteen hyponatremic patients with ODS (7 male and 7 female) were enrolled with a mean age of 62.7 ± 17.9 years old (from 28 to 92 years old). Delirium was the most common

initial presentation in 50% of patients (n = 7) followed by seizures (n = 2), unstable gait (n = 2), aphasia (n = 2), and drowsy consciousness (n = 1). Their associated comorbidities consisted of malnutrition (n = 6), diabetes (n = 3), chronic kidney disease (n = 3), depression (n = 3), head injury (n = 2), and hypertension (n = 1). Laboratory findings showed serum Na^+ was 107.2 ± 1.2 mmol/L with low serum osmolality of 255.3 ± 8.0 mOsm/kgH_2O, hypokalemia (K^+, 3.1 ± 0.7 mmol/L), hypophosphatemia (phosphorus, 2.3±1.0 mg/dL), hypocalcemia (total calcium, 7.9±0.7 mg/dL), and hypoalbuminemia (albumin, 3.4 ± 0.6 g/dL), indicating gastrointestinal losing with malnutrition in these patients. Metabolic alkalosis ($HCO3^-$, 27.3 ± 6.8 mmol/L) and hypochloremia (Cl^-, 83.3 ± 9.3 mmol/L) were also presented. Table 2 shows that associated underlying causes of hyponatremia consisted of gastrointestinal illness with poor intake (n = 7), chronic use of diuretics (n = 2), syndrome of inappropriate antidiuretic hormone (n = 2), pneumonia (n = 2), and hypopituitarism (n = 1). Compared with patients without gastrointestinal illness, there were relatively lower serum phosphorus (1.9 ± 0.6 vs. 3.0 ± 1.4 mg/dL), albumin (3.2 ± 0.7 vs. 3.6 ± 0.5 g/dL), and urine osmolality (318 ± 202 vs. 382 ± 178 mOsm/L) in patients with gastrointestinal illness, and both of them had hypokalemia (3.1 ± 05. vs.

Table 1: Clinical and laboratory characteristics in osmotic demyelination syndrome patients with chronic hyponatremia (n=14)

Clinical characteristics		
Age (years old)		62.7±17.9
Gender (male/female)		7/7
Body weight (kg)		51.4±10.6
Height (cm)		157.6±4.9
SBP (mmHg)		120.9±15.3
DBP (mmHg)		74.8±6.9
Initial presentation, n (%)		
Delirium		7 (50.0)
Seizure		2 (14.2)
Unstable gait		2 (14.2)
Aphasia		2 (14.2)
Drowsy consciousness		1 (7.1)
Associated comorbidities		
Malnutrition		6
Diabetes		3
Chronic kidney disease		3
Depression		3
Head injury		2
Hypertension		1
Laboratory data Serum	Reference	Data
Osmolality	275-295 mOsm/kgH_2O	255.3±8.0
Sodium	135-142 mmol/L	107.2±1.2
Potassium	3.5-5.0 mmol/L	3.1±0.7
Chloride	98-106 mmol/L	83.3±9.3
Phosphorus	2.6-4.5 mg/dL	2.3±1.0
Total calcium	8.4-10.2 mg/dL	7.9±0.7
Magnesium	1.7-2.55 mg/dL	2.1±0.1
Albumin	3.5-5.7 g/dL	3.4±0.6
Glucose	74-103 mg/dL	113.4±25.4
Triglyceride	−200 mg/dL	76.3±30.9
Cholesterol	−200 mg/dL	143.3±35.1
BUN	7-20 mg/dL	17.8±13.5
Creatinine	0.7-1.2 mg/dL	1.0±0.8
Hemoglobin	13.5-18.0 g/dL	11.9±1.3
$HCO3^-$	22-26 mmol/L	27.3±6.8

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, $HCO3^-$ Bicarbonate

Table 2: Underlying causes and clinical features in patients with osmotic demyelination syndrome

	Number of patients, n (%)
Underlying causes	
Gastrointestinal illness with poor intake	7 (50.0)
Chronic use of diuretics	2 (14.2)
SIADH	2 (14.2)
Pneumonia	2 (14.2)
Hypopituitarism	1 (7.1)
Localization of brain lesion	
CPM	6 (42.8)
EPM	4 (28.6)
Combined CPM and EPM	4 (28.6)
Admission to ICU	5 (35.7)
Mechanical ventilatory support	4 (28.6)
Clinical outcome	
Expired	1 (7.1)
Neurologic disability	9 (64.3)
Complete neurological recovery	4 (28.6)
Time to develop ODS	
<One day	1 (7.1)
1-2 days	2 (14.2)
2-3 days	5 (35.7)
3-4 days	3 (21.4)
4-5 days	3 (21.4)

SIADH: Syndrome of inappropriate antidiuretic hormone; CPM: Central pontine myelinolysis; EPM: Extrapontine myelinolysis; ICU: Intensive care unit, ODS: Osmotic demyelination syndrome

3.1 ± 0.8 mmol/L). As for management, most patients (n = 9) were treated with normal saline, but hypertonic saline (3% saline) was also administrated in two patients.

Radiologic findings

Although CPM and EPM share the same pathogenesis, the location of lesions could result in different clinical manifestations. In the literature, more than half patients had CPM alone, while 31.1% of patients had both CPM and EPM, and only 12.8% patients had only EPM.[21] The radiological findings demonstrated that isolated CPM and EPM were noted in 42.8% and 28.6% of ODS patients, respectively, and the remainders had combined both CPM and EPM involvement [Table 2]. A typical illustration of CPM/EPM is shown in Figure 1 with high T2 Mexican hat-shaped signal within the central pons with sparing of the corticospinal tracts ventrolaterally [Figure 1a and 1b] and bilateral symmetric high-signal intensity in the thalamus [Figure 1c] and putamen [Figure 1d] in T2/FLAIR MRI.

Clinical outcome

Regarding the clinical outcome among all ODS patients, five patients (35.7%) were admitted to the ICU for intensive care and four of them needed mechanical ventilatory support. ODS developed frequently after 2–3 days (n = 5, 35.7%), followed by 3–4 and 4–5 days (n = 3, 21.4%). There were nearly 43% of ODS patients having unfavorable outcome and poor prognosis including death (n = 1) and disability (n = 9). Nevertheless, the other four patients recovered completely without sequelae [Table 2]. There were four patients with rapid Na^+ correction rate of more than 12 mmol/L/day and only two patients received dDAVP and dextrose infusion for rescue therapy, respectively, but they still developed neurological sequalae such as drowsy consciousness, delirium, and aphasia.

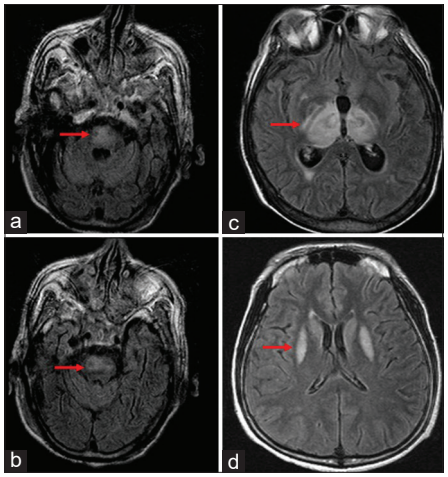

Figure 1: Representative typical brain magnetic resonance imaging findings in central pontine myelinolysis (a and b), extrapontine myelinolysis (c and d). T2/fluid attenuated inversion recovery magnetic resonance imaging showing high T2 mexican hat shaped signal (red arrow) within the central pons with sparing of the corticospinal tracts ventrolaterally (a and b) and bilateral symmetric high-signal intensity (red arrow) in the thalamus (c) and putamen (d)

The effect of rapid Na^+ correction rate

Their mean Na^+ correction rate was 8.4 ± 3.9 mmol/L/day (3.7–14.0 mmol/L/day). In patients with rapid Na^+ correction rate of more than 12 mmol/L/day (n = 4), their mean rate was 13.2 ± 0.7 mmol/L/day and they had significant hypokalemia (serum K^+ 2.5 ± 0.4 vs. 3.5 ± 0.7 mmol/L, $P < 0.05$) shown in Figure 2. There was no statistical significance in BUN, Creatinine, Glucose, Na^+, phosphorus, total Ca^{2+}, albumin, and hemoglobin between these two groups. When rapid Na^+ correction rate was defined as more than 10, 8, and 6 mmol/L/day based on different guidelines, there was no statistical significance in serum K^+ between patients with rapid Na^+ correction rate and those without using cutoff value of 10, 8, and 6 mmol/L/day shown in Figure 3.

DISCUSSION

In this study, we retrospectively characterized the underlying causes, clinical features, laboratory data, radiologic findings, and risk factors in hyponatremic patients with ODS. We found that patients with malnutrition and certain electrolytes deficiency such as K^+ and phosphorus were more susceptible to develop ODS. Most patients occurred earlier after 3 days of saline treatment. Common features included delirium and seizure and most of them had unfavorable outcome. CPM alone was predominant lesion of ODS based on radiologic finding. Although the average Na^+ correction rate was limited within recommended rate, four patients still had rapid Na^+ correction rate (more than 12 mmol/L/day). Of note, these patients with rapid Na^+ correction rate had significant hypokalemia compared with those without. Table 3 summarizes the literature review of clinical characteristics, risk factors, and clinical outcome in patients with ODS. Although we only enrolled 14 patients, our study was still the second largest ODS patients and had similar findings in onset day of ODS, risk factors, clinical outcome, and radiological finding. Nevertheless, our patients had lower Na^+ correction rate compared with others (approximately 8 vs. 21 mmol/L/day), confirming that ODS still developed even achieving the limit of Na^+ correction rates.

Our study points out that hypokalemia is a major risk factor in chronic hyponatremic patients with ODS, and it is also associated with rapid Na^+ correction rate. Therefore, hypokalemia seems to play a contributory role in the pathogenesis of ODS.[24] Hypokalemia *per se* is associated with a decreased concentration of Na^+-K^+-activated adenosine

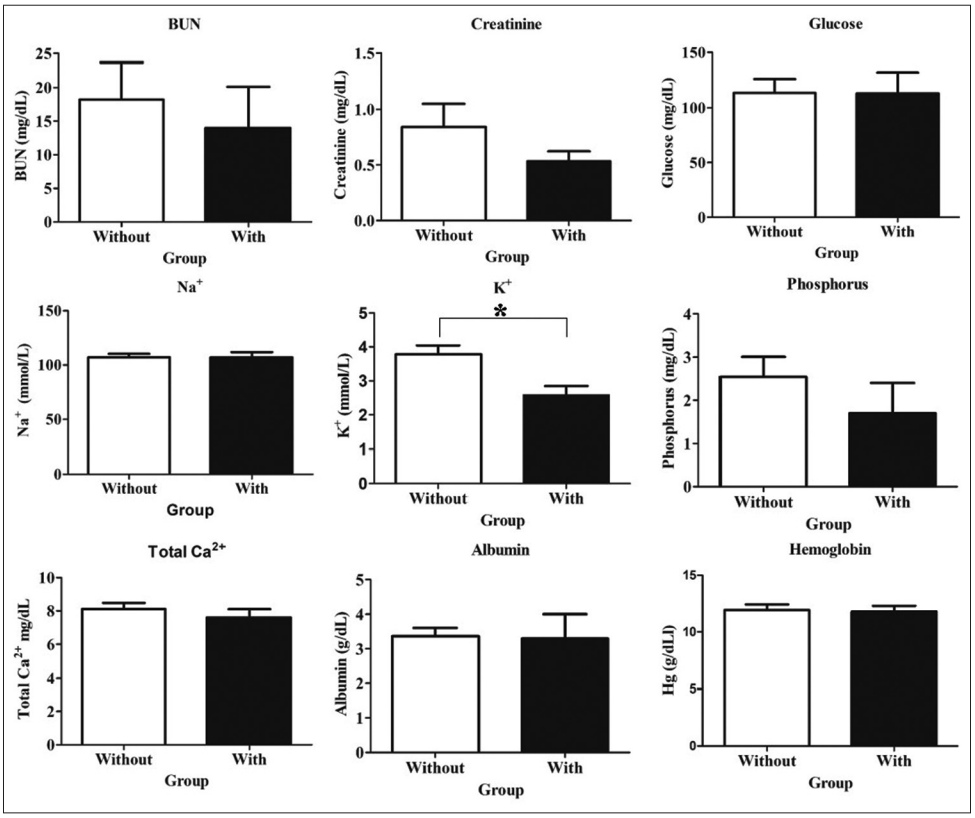

Figure 2: Comparison of laboratory biochemistries in osmotic demyelination syndrome patients between without rapid Na^+ correction (<12 mmol/L/day) ($n = 10$) and with rapid Na^+ correction (more than 12 mmol/L/day) ($n = 4$). The black column denotes patients with rapid Na^+ correction and the white column, those without. *Denotes $P < 0.05$

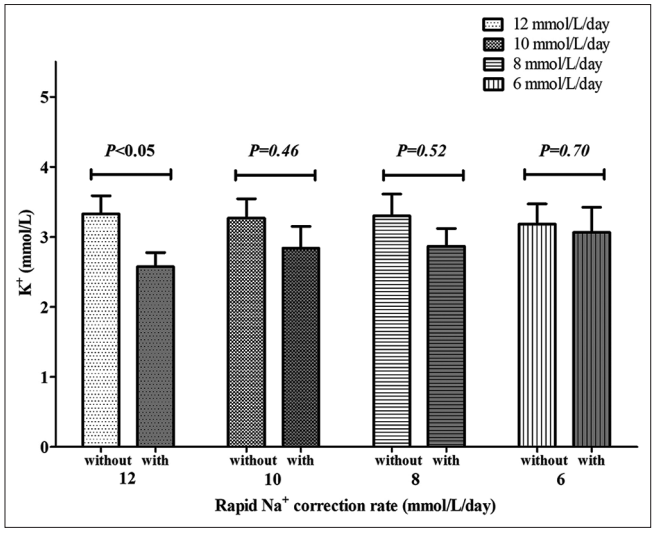

Figure 3: Serum potassium (K^+) difference between without Na^+ rapid correction and with Na^+ rapid correction in osmotic demyelination syndrome patients. The cutoff value of Na^+ rapid correction was defined as 12, 10, 8, and 6 mmol/L/day, respectively, based on different guidelines

triphosphate (ATP) (Na^+-K^+-ATPase) in endothelial or glial cell membranes. A decrease in Na^+-K^+-ATPase activity during hypokalemia may affect the cell's ability to preserve its volume and predispose the cell to injury by osmotic stress associated with the rapid rise in the Na^+ concentration.[25] Moreover, K^+ administration can increase serum Na^+ concentration because supplement of KCl can lead to the influx of K^+ into cells allowing exit of Na^+ into the extracellular space, resulting increased extracellular Na^+ concentration.[26] Based on our finding, the concomitant with hyponatremia and hypokalemia is the potential risk factor associated with developing ODS regardless of Na^+ correction rate. Therefore, clinicians should consider K^+ supplement as a molar equivalent of Na^+ while maintaining adequate Na^+ correction rate and limit the Na^+ correction rate to less than recommended rate. Identifying the underline causes of hypokalemia with appreciate management is crucial in patients with chronic hyponatremia.

In addition to hypokalemia, other risk factors include malnutrition and gastrointestinal illness with loss of divalent cation. Our study showed that hypoalbuminemia and hypophosphatemia were common findings in hyponatremic patients with ODS. Indeed, hypophosphatemia has been reported as a risk factor of ODS,[27,28] though the pathogenesis remains unclear. Cell volume is tightly regulated under normal

Table 3: Literature review of clinical characteristics, risk factors, and clinical outcome in patients with osmotic demyelination syndrome

	Design and subjects	ODS patients	Onset of ODS	Na^+ correction rate in ODS patients	Risk factors	Clinical outcome	Brain lesion
George *et al*.[22]	Retrospective, 1490 hyponatremic patients (Na^+ <120 mmol/L)	17	NA	> 8 mmol/L/day in 7 ODS patients	Hypovolemia, beer potomania, malnutrition, and hypokalemia	12 patients with neurologic deficit	CPM (*n*=4), CPM + EPM (*n*=5)
Sterns *et al*.[15]	Case series, 60 hyponatremic patients (Na^+ <116 mmol/L)	8	Day 3 (*n*=3), day 4 (*n*=2)	21.5±5.0 mmol/L/day	Use of diuretics and diarrhea	8 patients with neurologic sequalae	CPM (*n*=2), EPM (*n*=1), CPM + EPM (*n*=1)
Musana and Yale[23]	Retrospective	6	NA	NA	Chronic alcoholism (*n*=5)	5 patients with neurologic deficit	CPM (*n*=4), CPM + EPM (*n*=2)
Vu *et al*.[11]	Retrospective, 225 hyponatremic patients (Na^+ <120 mmol/L)	4	Day 4±2	21.0±5.0 mmol/L/day	Younger, abuse alcohol, hypokalemia	All with residual neurological disability	CPM (*n*=4)
Geoghegan *et al*.[12]	Retrospective, 412 hyponatremic patients (Na^+ <120 mmol/L)	1	Day 1	21 mmol/L/day	Psychogenic polydipsia	NA	NA
This study	Retrospective	14	Day 3 (*n*=5)	8.4±3.9 mmol/L/day	Hypokalemia, malnutrition	9 patients with neurologic disability, and 1 expired	CPM (*n*=6), EPM (*n*=4) CPM + EPM (*n*=4)

CPM: central pontine myelinolysis; EPM: extrapontine myelinolysis, ODS: Osmotic demyelination syndrome, NA: Not applicable

conditions such as constant supplement of glucose, ATP for energy-driven amino acid, and electrolyte transports.[29] In response to the induction of an acute relative extracellular hyperosmolar state during Na^+ administration, cells can be expected to undergo free water loss in the first few hours, followed by intracellular accumulations of Na^+, K^+, and Cl^-, and existing/eventual synthesis of new amino acids.[26,30] Therefore, malnutrition with metabolic deficiency such as hypoalbuminemia, hypophosphatemia, and other vitamin or amino acid deficiencies may affect the intracellular response to the rapid rise in extracellular osmolality. Recently, it has been shown that hyponatremia leads to downregulation of a neutral amino acid transporter that impairs cellular reuptake of amino acids, rendering them more susceptible to injury when hyponatremia is corrected. Early identification of nutritional status and prompt nutritional support with protein and amino acid should be suggested.

Despite the causative risk factors, Na^+ correction rate has been traditionally emphasized as the major determinants in the development of ODS. However, the optimal Na^+ correction rate remains controversial. Previous guidelines of Na^+ correction rates are suggested to less than 12 mmol/L/day.[15] However, recent guidelines have recommended that Na^+ correction rate should be less than 10 or 8 mmol/L/day when there is a high risk of ODS.[18] Moreover, Geoghegan *et al*. reported 51% of severe hyponatremic patients underwent optimal correction of Na^+ (6–10 mmol/L/day).[12] More recent studies have proposed that Na^+ correction rate should be less rapid with rates of 4–6 mmol/L/day.[31,32] Most of our patients had acceptable Na^+ correction rate, but four patients still had rapid Na^+ correction rate of more than 12 mmol/L/day. Among patients with rapid correction rate, hypokalemia is the major risk factor of ODS development, and patients with severe hypokalemia are prone to developing rapid change of serum Na^+.

Our study still has several limitations. First, this study was designed retrospectively, and our study population was relatively small. Second, we could not obtain the real incidence because of lacking control group of profound hyponatremia (Na^+ <120 mmol/L) without ODS. Third, the retrospective study did not provide other detailed laboratory data (such as plasma renin activity and aldosterone), volume status evaluation, intake and urine output, and management strategies during management.

CONCLUSION

Malnutrition along with concomitant electrolyte deficiencies, especially hypokalemia seems to play a contributory role in the development of ODS in patients with chronic hypokalemia. Clinicians should timely recognize these potential risks with limited Na^+ correction rate in high-risk patients to avoid neurologic deficit and catastrophic outcomes.

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Conflicts of interest

There are no conflicts of interest.

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