Osmotic Demyelination Syndrome Following Correction of Hyponatremia by ≤10 mEq/L per day

Srijan Tandukar¹, Richard H. Sterns², Helbert Rondon-Berrios³

¹Willis-Knighton Medical Center, Shreveport, LA
²University of Rochester School of Medicine and Dentistry, Rochester, NY
³Renal-Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, PA

Correspondence to:
Helbert Rondon-Berrios, MD, MS
Renal-Electrolyte Division
University of Pittsburgh School of Medicine
3550 Terrace St
A915 Scaife Hall
Pittsburgh, PA 15261
Telephone: 412-647-2130
E-mail address: rondonberriosh@upmc.edu
Key Points

- ODS can occur despite adherence to current hyponatremia correction guidelines, especially in patients with SNa <115 mEq/L.
- Limit the rate of correction of SNa <8 mEq/L in any 24h period in these patients to minimize the risk of ODS.
- Thiamine supplementation should be considered for any hyponatremic patient whose dietary intake has been poor.

Abstract

Background: Overly rapid correction of chronic hyponatremia may lead to osmotic demyelination syndrome. European guidelines recommend a correction to ≤10 mEq/L in 24 hours to prevent this complication. However, osmotic demyelination syndrome may occur despite adherence to these guidelines.

Methods: We searched the literature for reports of osmotic demyelination syndrome with rates of correction of hyponatremia ≤10 mEq/L in 24 hours. The reports were reviewed to identify specific risk factors for this complication.

Results: We identified 19 publications with a total of 21 patients that were included in our analysis. The mean age was 52 years of which 67% were male. All of the patients had community acquired chronic hyponatremia. Twelve patients had an initial serum sodium <115 mEq/L, of which seven had an initial serum sodium ≤105 mEq/L. Other risk factors identified included alcohol use disorder (n=11), hypokalemia (n=5), liver disease (n=6), and malnutrition.
The maximum rate of correction in patients with serum sodium <115 mEq/L was at least 8 mEq/L in all but 1 patient. In contrast, correction was <8 mEq/L in all but 2 patients with serum sodium ≥115 mEq/L. Among the latter group, osmotic demyelination syndrome developed before hospital admission or was unrelated to hyponatremia overcorrection. Four patients died (19%), 5 had full recovery (24%) and 9 (42%) had varying degrees of residual neurological deficits.

Conclusion: Osmotic demyelination syndrome can occur in patients with chronic hyponatremia with a serum sodium <115 mEq/L despite rates of serum sodium correction ≤10 mEq/L in 24 hours. In patients with severe hyponatremia and high risk features, especially those with serum sodium <115 mEq/L, we recommend limiting serum sodium correction to <8 mEq/L. Thiamine supplementation is advisable for any hyponatremic patient whose dietary intake has been poor.
Introduction

To avoid the osmotic demyelination syndrome (ODS) following treatment of chronic hyponatremia a number of therapeutic limits have been proposed. The American Expert Panel Recommendations endorse a serum sodium (SNa) correction limit of 10 to 12 mEq/L in any 24-hour and 18 mEq/L in any 48-hour period for patients at average risk of ODS and 8 mEq/L in any 24-hour period for patients at high risk of ODS, while the European Clinical Practice Guidelines recommend a daily limit of SNa correction of 10 mEq/L in the first 24 hours and 8 mEq/L during every 24 hours thereafter. In this study, we review reported cases of ODS that occurred after correction of hyponatremia by ≤10 mEq/L in the first 24 hours to identify the risk factors that predispose to ODS despite adherence to the European Clinical Practice Guidelines.

Methods

We searched PubMed using terms ‘osmotic demyelination syndrome’, ‘central pontine myelinolysis’ and ‘slow correction of hyponatremia’ to identify English language cases of patients with hyponatremia who developed ODS despite a SNa correction rate of 10 mEq/L or lower in 24 hours. We then reviewed all studies and case reports cited by the articles identified in our PubMed search. We only included studies if the rate of correction had been documented to be 10 mEq/L or lower in the first 24 hours of treatment followed by clinical or radiologic evidence of ODS. We excluded studies reporting the rate of correction in mEq/L per hour, or as an average value over several days, unless the daily change in SNa was explicitly stated. We also excluded studies reporting on multiple patients unless changes in SNa were provided for individual patients.
Whenever available we recorded data on age, sex and race, comorbidities and medications. We assumed hyponatremia to be chronic if it developed in the community and was present on admission or if it was hospital-acquired with documentation of a normal SNa >48 hours prior to its treatment.

The initial SNa, serum potassium, creatinine, blood urea nitrogen levels along with other laboratory chemistries, serum and urine osmolalities, and urine electrolyte studies were recorded whenever available. The change in SNa in the first 24 hour and 48 hour period along with the absolute SNa values were recorded. The approach to treatment of hyponatremia was reviewed. The administration of intravenous fluids - whether isotonic or hypertonic saline – the rate of infusion, volume infused, bolus versus continuous therapy with or without use of desmopressin was recorded. Other approaches to treatment including fluid restriction, loop diuretics, salt tablets, urea, and vasopressin antagonists were noted.

From the case histories, we recorded the nature of symptoms before treatment of hyponatremia, the day of onset of symptoms suggestive of ODS, the course of ODS symptoms, MRI findings and the presence or absence of residual sequelae or a fatal outcome.

The presence of risk factors for ODS such as SNa≤105 mEq/L, alcohol use disorder, hypokalemia, liver disease with or without cirrhosis, malnutrition, and history of liver transplantation was noted for each patient. The presence of factors that would predispose to overly rapid correction of hyponatremia were recorded when available such as treatment of low dietary solute intake, treatment of hypovolemia, treatment of cortisol deficiency, resolution of transient syndrome of inappropriate antidiuresis (SIAD), discontinuation of thiazides and other causative medications of SIAD, and use of vasopressin antagonists. Any high risk features of brain herniation were recorded such as self-induced water intoxication (e.g., psychogenic
polydipsia, ecstasy use, and endurance exercise), acute postoperative state, and underlying intracranial pathology.

Results

Selection of studies for analysis

A total of 21 patients met inclusion criteria, 18 patients from 17 case reports and 3 patients from 2 retrospective observational case series.

Patient characteristics and clinical presentation

The mean age of the patients was 52 years (Range 26 to 74 years) and 67% were male. Only two reports mentioned the patient’s race or ethnicity (one white and one Hispanic). There was a wide variation in the patients’ presenting complaints. Confusion and weakness were the most common complaints.

Hyponatremia and rates of correction

All of the patients had community-acquired hyponatremia. The initial mean SNa was 111 mEq/L (range 94 to 130 mEq/L). Initial serum potassium values were only reported in 6 patients, 5 of whom were hypokalemic (2.1 to 3.2 mEq/L). Initial serum and urine osmolalities were reported in only 6 patients and ranged from 197 to 238 mOsm/kg and 97 to 452 mOsm/kg respectively. Urine sodium values were reported in 4 patients, and ranged from 3 to 53 mEq/L.

The rate of correction of hyponatremia at 24 and 48 hours ranged from 2 to 10 mEq/L and 5 to 18 mEq/L, respectively (Figure 1). Consistent with most reports of ODS, 12 of the patients had initial SNa <115 mEq/L (range 94 to 112 mEq/L). The maximum rate of correction in this group was at least 8 mEq/L in all but one of these patients (Table 1). By contrast,
correction was less than 8 mEq/L in all but 2 patients with less severe hyponatremia (range 115 to 130 mEq/L) (Table 2).

Treatment approach to hyponatremia

Hypertonic saline was given to 4 patients (3% saline in 3 patients, 2.5% saline in 1 patient). Normal saline was given in 11 patients. Other treatment modalities such as cessation of thiazide diuretics, fluid restriction and oral salt tablets were used in various combinations. (Table 3 & 4)

ODS and its clinical course

ODS occurred 2 to 16 days after correction of hyponatremia. One patient was described as asymptomatic and in 2 cases, no description of ODS features were provided. Eighteen patients presented with classic features of ODS: spasticity, hyperreflexia, quadriplegia, mutism, dysarthria, gait abnormalities, obtundation and coma while 1 patient was asymptomatic and clinical features were not described in 2 patients. Psychotic features were reported in 3 patients. Respiratory failure requiring intubation was seen in 2 patients and another patient with hematemesis was intubated for airway protection. In all but 1 patient, the clinical diagnosis of ODS was confirmed by brain MRI findings of demyelination (9 pontine, 2 extrapontine, 7 pontine and extrapontine, and 2 unstated). Four patients (19%) died following the diagnosis of ODS. Complete resolution of ODS symptoms was seen in 5 patients (24%) with 9 patients (42%) showing varying degrees of residual deficits. (Tables 1 & 2).

Risk factors for ODS
Among the risk factors for ODS, a SNa ≤105 mEq/L was reported in 7 patients, hypokalemia in 5, malnutrition in 11, alcohol use disorder in 11, and liver disease in 6 (Figure 2). None of the patients had a liver transplant. Factors predisposing to overly rapid correction of hyponatremia included low dietary solute intake in 5 patients, hypovolemia in 7, and discontinuation of diuretics in 3.

Discussion

The appropriate rates of correction of SNa in hyponatremia to prevent neurological complications has been an area of debate for decades. The European Clinical Practice Guidelines state that the SNa should be limited to ≤10 mEq/L in the initial 24 hours and ≤8 mEq/L per day in subsequent day. However, our literature review identified many cases of well documented ODS, in which the rate of correction of SNa was reported to adhere to these guidelines (Tables 1 and 2).

We divided our cases, somewhat arbitrarily, into two groups: 12 patients with SNa <115 mEq/L (Table 1) and 9 patients with SNa ≥115 mEq/L (Table 2). We believe that findings in the group with SNa <115 mEq/L (range 94 to 112 mEq/L) are most relevant to clinicians attempting to set an appropriate correction limit. In a literature review, Spasovski et al found that 96% (52/54) of patients with ODS had an initial SNa < 120 mEq/l, and 85% (46/54) had a SNa < 115 mEq/L.² Among hospitalized patients with hyponatremia, a SNa <115 mEq/L is less than half as common as a SNa between 115 and 119 mEq/L and about one ninth as common as a SNa between 120 and 124 mEq/L.⁵ Therefore, since about 85% of patients with ODS have a SNa <115 mEq/L, the risk of ODS in a patient with a SNa <115 mEq/L is more than 10-fold greater than the risk in a patient with a higher SNa.
The 12 patients with SNa<115 mEq/L had a median SNa of 103 mEq/L and all but one had risk factors that made them more susceptible to injury caused by a rapid increase in SNa (SNa≤105 mEq/L, alcohol use disorder, hypokalemia, liver disease, and malnutrition). Characteristics of this group were similar to those identified in a nationwide study of 83 patients diagnosed with ODS in Sweden; in that study, most patients (86.7%) were hyponatremic (all chronic) with a median serum sodium of 104 mEq/L (IQR 99.5 -110.5); 69% of the patients were alcoholic, and 67.5% were hypokalemic. Of note, Swedish national guidelines set a correction limit of SNa to ≤ 8 mEq/L in 24 hours, and all but 6 of the 83 patients (7%) exceeded this rate of correction. The cases we identified represent a small percentage of the cases published in the literature, but they confirm that ODS can occur when severe, chronic hyponatremia is corrected by ≤10 mEq/L or even by 8 mEq/L per 24 hours.

The susceptibility to ODS associated with extremely low SNa can be explained by the brain’s adaptation to hyponatremia. The fall in effective plasma tonicity that accompanies hyponatremia leads to the movement of water into brain cells, primarily astrocytes, which may lead to cerebral edema when hyponatremia is acute and severe. The dreaded complications of cerebral edema include seizures, obtundation, coma, brain herniation and death. When hyponatremia develops more gradually, over 48 hours or longer, the brain adapts such that the brain cells restore its normal volume by loss of potassium within the first 3 hours, and then organic osmolytes including myo-inositol, glutamine, glutamate, taurine, glycine, aspartate and creatine. When SNa falls below 105 mEq/L, survival is not possible without the adaptive loss of organic osmolytes. Overly rapid correction of chronic hyponatremia is known to cause ODS with its attendant neurologic manifestations which may be irreversible. Astrocytes play a critical role in maintaining the production, function and maintenance of myelin-producing
oligodendrocytes. They regulate neuroglial communication, neuronal excitability and neurotransmission. The inability of the astrocytes to maintain intracellular volume homeostasis to changing extracellular osmolality is a key factor in the pathogenesis of ODS.\textsuperscript{9}

Correction of chronic hyponatremia subjects the astrocytes to hyperosmotic stress as they try to compensate for a rising extracellular osmolality by movement of osmolytes, mainly myo-inositol and glutamine/glutamate back into the cell in an effort to prevent excessive cell shrinkage, injury and apoptosis. When this osmoregulatory function of the astrocytes is disrupted, it leads to degeneration of both the myelin and oligodendrocytes resulting in the clinicopathologic syndrome of ODS. These intracellular responses require phosphate, often in the form of adenosine triphosphate (ATP), along with other substrates including amino acids, glucose, potassium and magnesium.\textsuperscript{10} Patients who are malnourished and have a history of alcohol use disorder are often chronically deficient in these substrates and therefore, may not be able to mount a compensatory response adequate to prevent glial cell shrinkage, apoptosis and osmotic demyelination. Moreover, Häussinger et al, using proton magnetic resonance spectroscopy, demonstrated marked depletion of brain myo-inositol stores in both cirrhosis with hepatic encephalopathy and in chronic hyponatremia.\textsuperscript{11}

Potassium ions act as effective osmoles like sodium ions. A hypokalemic state may jeopardize the early protective phase of the glial cells to hyperosmotic stress by the inability to rapidly move potassium ions into the cells to prevent intercompartmental osmolality difference.\textsuperscript{12} In addition, hypokalemia prevents insulin release that is vital for glucose uptake by glial cells and generation of ATP that drives the cellular response to hyperosmotic stress.\textsuperscript{10} Correction of hypokalemia may also lead to overly rapid correction of hyponatremia and ODS independent of other factors.\textsuperscript{13} The severity of hyponatremia is directly proportional to the risk of ODS as lower
levels of SNa are more likely to be associated with overly rapid correction of hyponatremia and consequent ODS. The risk appears highest with SNa ≤ 105 mmol/L.\textsuperscript{14,15}

Nine of the reported patients that we identified had SNa ≥ 115 mEq/L (115 to 130 mEq/L), including five with a SNa > 120 mEq/L, a level that is seldom associated with ODS (Table 2). At least two of these cases may have developed CPM before admission to the authors’ hospitals.\textsuperscript{3,16} One had been given intravenous fluids for gastroenteritis at a peripheral health center for two days and was transferred to the author’s hospital for altered consciousness.\textsuperscript{16} On admission, despite modest hyponatremia (120 mEq/L) the patient was stuporous and had bilateral Babinski signs. Another, with a SNa of 130 mEq/L on admission, was found to have asymptomatic CPM on a staging MRI for a newly diagnosed aggressive lymphoma.\textsuperscript{3} In addition to an unusually high SNa, six of the nine patients developed ODS despite extremely slow correction (no more than 4 to 6 mEq/L in 24 hours). Two of these cases were reported by the same author and both had other unusual features\textsuperscript{17}; both had severe, persistent vomiting, with poor dietary intake and untreated hyponatremia for over a month and both developed ODS despite azotemia (BUN 78 & 128 mg/dL, Creatinine 3.3 & 7 mg/dL), which is thought to protect against ODS from rapid correction of hyponatremia.\textsuperscript{18} These two patients and a similar atypical patient with end stage kidney disease\textsuperscript{19} and a SNa of 109 mEq/L (Table 1) who developed spastic quadriparesis and nystagmus after correction by only 5 mEq/L per day, may have had thiamine deficiency, which has been associated with CPM and EPM in patients who were not known to be hyponatremic.\textsuperscript{20} Another patient developed ODS after initially presenting with a SNa of 127 mEq/L;\textsuperscript{21} although the rate of correction never exceeded 10 mEq/L, he became severely hypernatremic, to a level of 161 mEq/L on the 7th day. ODS can be caused by hypernatremia even in the absence of hyponatremia\textsuperscript{22}; brain adaptations to even mild hyponatremia, would be expected to increase the
susceptibility to injury from hypernatremia. Two of the patients with SNa ≥115 mEq/L had hyperammonemia, one from cavernous transformation of the portal vein and one from end-stage liver disease. Patients with co-existing liver cirrhosis and chronic hyponatremia have swelling of the brain cells due to the combined effect of hyperammonemia and hypotonic hyponatremia. This is partly attributed to an increased level of intracellular glutamine in response to hyperammonemia with a compensatory loss of intracellular myo-inositol. Myo-inositol may serve as an anti-oxidant and has been shown to protect cells against osmotic stress in rats. In addition, patients with severe liver disease and hyperammonemia may develop lesions of CPM and EPM even in the absence of hyponatremia.

Our study has important limitations. First, we relied on data available in individual case reports that are likely to include patients with unusual findings. Second, several case reports of ODS that could have potentially affected the outcome of the study were excluded if they did not explicitly report the SNa corrections rates per 24 hour. Third, there is likely a publication bias. Fourth, the study is underpowered to draw any firm conclusions.

In conclusion, published reports of ODS despite slow correction of hyponatremia are more convincing for patients with SNa <115 mEq/L (Table 1) than for patients with higher SNa (Table 2). The latter cases include patients who may have already had CPM or EPM at the time of their admission and patients with uncommon conditions that by themselves can result in CPM or EPM even in the absence of hyponatremia; in such cases it is difficult to ascribe neurological complications to the very slow rise in SNa. Despite the limitations described, we believe that our findings can be useful in guiding treatment of patients with severe hyponatremia, especially those with SNa <115 mEq/L. In patients with conditions making them more susceptible to ODS (such as SNa ≤105 mEq/L, alcohol use disorder, hypokalemia, liver disease, malnutrition), well
documented ODS with a typical clinical course may complicate correction of chronic hyponatremia despite adherence to both the European Clinical Practice Guidelines (≤10 mEq/L per 24 hours) and to the recommendations of the American Expert Panel (≤8 mEq/L per 24 hours)\textsuperscript{1, 2}. It may therefore be prudent to take a more conservative approach to hyponatremia correction than has been recommended by current guidelines in this high-risk patient population as suggested by some experts.\textsuperscript{14, 27, 28} In such patients, we recommend limiting the rate of correction to \textit{less than} (not equal to) 8 mEq/L in any 24 hour period to minimize the risk of ODS. Thiamine deficiency is commonly present in patients with hyponatremia and it constitutes an etiology for ODS independent of hyponatremia.\textsuperscript{20} Thiamine supplementation, a low risk intervention, is advisable for any hyponatremic patient whose dietary intake has been poor.

**Disclosures:**

R. Sterns reports the following: Scientific Advisor or Membership: Section editor for Uptodate.

S. Tandukar reports the following: Other Interests/Relationships: American Society of Nephrology, American Society of Transplantation. The remaining author has nothing to disclose.

**Funding:**

Dr. Rondon-Berrios is funded by an exploratory/developmental research grant R21DK122023 from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institute of Health.

**Author Contributions:**

S Tandukar: Data curation; Investigation; Writing - original draft
R Sterns: Conceptualization; Formal analysis; Methodology; Writing - review and editing

H Rondon-Berrios: Conceptualization; Data curation; Formal analysis; Writing - original draft;
Writing - review and editing
References


10. Pham PM, Pham PA, Pham SV, Pham PT, Pham PT, Pham PC: Correction of hyponatremia and osmotic demyelinating syndrome: have we neglected to think intracellularly? Clin Exp Nephrol, 19: 489-495, 2015 10.1007/s10157-014-1021-y


<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>Initial SNa (mEq/L)</th>
<th>Factors Increasing Risk of ODS</th>
<th>ΔSNa at 24 hours (mEq/L)</th>
<th>ΔSNa at 48 hours (mEq/L)</th>
<th>Maximum ΔSNa (mEq/L/d)</th>
<th>ODS Symptoms (Onset)</th>
<th>Brain MRI</th>
<th>Final Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koul et al. 29</td>
<td>47/M</td>
<td>94</td>
<td>Hypokalemia</td>
<td>Not reported</td>
<td>Not reported</td>
<td>≤ 8*</td>
<td>Locked in (Day 3)</td>
<td>CPM &amp; EPM</td>
<td>Died of sepsis</td>
</tr>
<tr>
<td>de Souza et al. 30</td>
<td>50/M</td>
<td>98</td>
<td>None mentioned</td>
<td>4</td>
<td>13</td>
<td>9</td>
<td>Dysarthria, dysphagia, rigidity, normal reflexes, positive glabellar tap, grasp and palmmontal reflexes, bradykinetis, parkinsonian gait (Day 15)</td>
<td>CPM &amp; EPM</td>
<td>Mild gait dysfunction, urge incontinence</td>
</tr>
<tr>
<td>John et al. 8</td>
<td>65/F</td>
<td>100</td>
<td>None mentioned</td>
<td>8</td>
<td>16</td>
<td>8</td>
<td>Dysphasia, psychosis, dyskinesia (Day 3)</td>
<td>No lesions</td>
<td>Resolution</td>
</tr>
<tr>
<td>Leens et al. 31</td>
<td>54/F</td>
<td>100</td>
<td>Alcohol use disorder, Hypokalemia</td>
<td>10</td>
<td>18</td>
<td>10</td>
<td>Tetraplegic, pseudobulbar palsy, seizure, strabism (Day 5)</td>
<td>CPM &amp; EPM</td>
<td>Near complete recovery</td>
</tr>
<tr>
<td>Al-Shaibany et al.32</td>
<td>48/F</td>
<td>101</td>
<td>Alcohol use disorder, Liver disease</td>
<td>10</td>
<td>16</td>
<td>10</td>
<td>Leg weakness, scanning speech (Day 12)</td>
<td>CPM</td>
<td>Improved at discharge</td>
</tr>
<tr>
<td>Silbert et al. 33</td>
<td>51/F</td>
<td>101</td>
<td>None mentioned</td>
<td>10</td>
<td>14</td>
<td>10</td>
<td>Behavioral changes, dysarthria (Day 16)</td>
<td>CPM &amp; EPM</td>
<td>Partial resolution with residual pseudobulbar dysarthria</td>
</tr>
<tr>
<td>Rejinders et al. 34</td>
<td>57/M</td>
<td>105</td>
<td>Alcohol use disorder, Malnutrition</td>
<td>7</td>
<td>17</td>
<td>10</td>
<td>Dysphagia, ataxia, spasticity (Day 11)</td>
<td>CPM</td>
<td>Near complete recovery</td>
</tr>
<tr>
<td>Malhotra et al. 35</td>
<td>48/M</td>
<td>107</td>
<td>Alcohol use disorder, Liver disease, Malnutrition</td>
<td>8</td>
<td>16</td>
<td>8</td>
<td>Ataxia, dysarthria, weakness, spastic quadriparesis (Day 14)</td>
<td>CPM</td>
<td>Ataxia improved</td>
</tr>
<tr>
<td>Dellabarca et al. 36</td>
<td>63/M</td>
<td>109</td>
<td>Alcohol use disorder, Malnutrition</td>
<td>10</td>
<td>17</td>
<td>10</td>
<td>Dysarthria, dysphagia, bilateral cogwheel rigidity (Day 10)</td>
<td>CPM &amp; EPM</td>
<td>Death due to respiratory failure</td>
</tr>
<tr>
<td>Yamada et al. 39</td>
<td>61/F</td>
<td>109</td>
<td>None mentioned</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>Spastic tetraparesis, dysarthria, nystagmus, disturbed consciousness (Day 5)</td>
<td>CPM</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Macmillan et al. 4</td>
<td>70-74/M</td>
<td>111</td>
<td>Alcohol use disorder, Liver disease, Malnutrition, Hypokalemia</td>
<td>10</td>
<td>13</td>
<td>10</td>
<td>Symptoms not described by authors (Day 4)</td>
<td>Areas of lesions not specified</td>
<td>Unknown residual deficits</td>
</tr>
<tr>
<td>Dewitt et al. 37</td>
<td>37/F</td>
<td>112</td>
<td>Liver disease</td>
<td>9</td>
<td>17</td>
<td>9</td>
<td>Decerebrate posturing, disorientation, hyperreflexia, impaired horizontal eye movements (Day 4)</td>
<td>CPM</td>
<td>Improved with mild spasticity of lower extremities after 8 months</td>
</tr>
</tbody>
</table>

SNa=serum sodium concentration; ΔSNa=Change in SNa; ODS=osmotic demyelination syndrome; CPM=central pontine myelinolysis, EPM=extrapontine myelinolysis

*Correction did not exceed 8 mEq/L on any day; precise values not provided; treated with 3% saline until SNa reached 120 mEq/L.
Table 2. Patients with Initial Serum Sodium ≥115 mEq/L Who Experienced Osmotic Demyelination Syndrome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>Initial SNa (mEq/L)</th>
<th>Factors Increasing Risk of ODS</th>
<th>∆SNa at 24h (mEq/L)</th>
<th>∆SNa at 48h (mEq/L)</th>
<th>Maximum ∆SNa (mEq/L/d)</th>
<th>ODS Symptoms (onset)</th>
<th>Brain MRI</th>
<th>Final Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al.(^{23})</td>
<td>30/M</td>
<td>115</td>
<td>High ammonia levels</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>Dysarthria, dysphagia, exaggerated deep tendon reflexes (Day 2)</td>
<td>EPM</td>
<td>No improvement</td>
</tr>
<tr>
<td>Pradhan et al.(^{17})</td>
<td>55/M</td>
<td>115</td>
<td>Malnutrition</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>Spastic quadripareis, brisk deep tendon reflexes, positive Babinski in right (Day 8)</td>
<td>CPM</td>
<td>No improvement, patient death</td>
</tr>
<tr>
<td>Macmillan et al.(^{4})</td>
<td>60-64/M</td>
<td>115</td>
<td>Alcohol use disorder, Liver disease, Malnutrition</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>Symptoms not described by authors (Day 12)</td>
<td>Areas of lesions not specified</td>
<td>Unknown residual deficits</td>
</tr>
<tr>
<td>Pradhan et al.(^{17})</td>
<td>39/M</td>
<td>118</td>
<td>Malnutrition</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>Dysarthria, dysphagia, rigidity, impaired horizontal eye movement, decorticate posturing, brisk deep tendon reflexes, positive Babinski bilaterally (Day 6)</td>
<td>CPM &amp; EPM</td>
<td>Incomplete recovery. Able to feed himself, speak few words, walk with support. Cogwheel rigidity and Parkinsonian gait persisted</td>
</tr>
<tr>
<td>Zunga et al.(^{16})</td>
<td>65/F</td>
<td>121</td>
<td>Hypokalemia</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>Altered sensorium, stuporous (On admission)</td>
<td>EPM</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Orakzai et al.(^{38})</td>
<td>52/M</td>
<td>122</td>
<td>Alcohol use disorder, Malnutrition</td>
<td>8</td>
<td>16</td>
<td>8</td>
<td>Non-verbal, decreased right hand grip strength, paralysis of other extremities, Babinski positive bilaterally, pupillary responses sluggish (Day 5)</td>
<td>CPM</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Jahan et al.(^{39})</td>
<td>55/M</td>
<td>123</td>
<td>Alcohol use disorder, Malnutrition</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>Encephalopathic, dysarthria, dysphagia, ophthamoplegia, brisk deep tendon reflexes in all extremities (Day 7)</td>
<td>CPM &amp; EPM</td>
<td>Dysarthria, dysphagia, neurological exam improved ‘significantly’</td>
</tr>
<tr>
<td>Davenport et al.(^{21})</td>
<td>63/M</td>
<td>127</td>
<td>Alcohol use disorder, Hypokalemia, Malnutrition</td>
<td>9</td>
<td>15</td>
<td>10</td>
<td>Obtundation, comatose (Day ?)</td>
<td>CPM</td>
<td>Death</td>
</tr>
<tr>
<td>Shah et al.(^{3})</td>
<td>26/M</td>
<td>130</td>
<td>Alcohol use disorder, Liver Disease, Malnutrition</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>Never develop ODS symptoms</td>
<td>CPM (MRI done to evaluate lymphoma)</td>
<td>Remained asymptomatic</td>
</tr>
</tbody>
</table>

SNa=serum sodium concentration; ∆SNa=Change in SNa; ODS=osmotic demyelination syndrome; CPM=central pontine myelinolysis, EPM=extrapontine myelinolysis
<table>
<thead>
<tr>
<th>Reference</th>
<th>Etiology of hyponatremia</th>
<th>Treatment of hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koul et al.</td>
<td>Not mentioned by authors, presumably from a vasopressin-mediated process with reduced effective arterial blood volume</td>
<td>3% saline till SNa reached 120, then NS given</td>
</tr>
<tr>
<td>de Souza et al.</td>
<td>Vomiting from colchicine administration</td>
<td>Not mentioned by authors</td>
</tr>
<tr>
<td>John et al.</td>
<td>SIAD secondary to small cell bronchogenic carcinoma of lung</td>
<td>Saline infusion (not specified as 3%), discontinuation of thiazide diuretic</td>
</tr>
<tr>
<td>Leens et al.</td>
<td>Psychogenic polydipsia, thiazide diuretic use</td>
<td>Water restriction, NS with potassium added</td>
</tr>
<tr>
<td>Al-Shaibany et al.</td>
<td>Watery diarrhea and vomiting</td>
<td>3% saline at 150 ml bolus, then NS 50-100 ml/h</td>
</tr>
<tr>
<td>Silbert et al.</td>
<td>Psychogenic polydipsia</td>
<td>Hypertonic saline 2.5% and fluid restriction</td>
</tr>
<tr>
<td>Reijnders et al.</td>
<td>Thiazide diuretic use and poor intake</td>
<td>Discontinuation of thiazide diuretic, isotonic saline infusion</td>
</tr>
<tr>
<td>Malhotra et al.</td>
<td>Excess fluid and low solute intake</td>
<td>Fluid restriction</td>
</tr>
<tr>
<td>Dellabarca et al.</td>
<td>Not mentioned by authors, presumably from low solute intake</td>
<td>Intravenous saline infusion (not specified as 3%), water restriction</td>
</tr>
<tr>
<td>Yamada et al.</td>
<td>Excess vasopressin stimulated by vomiting</td>
<td>Continuous infusion of 3% saline at 25 ml/h</td>
</tr>
<tr>
<td>Macmillan et al.</td>
<td>Not mentioned by authors</td>
<td>Desmopressin</td>
</tr>
<tr>
<td>Dewitt et al.</td>
<td>Not mentioned by authors</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

NS=NaCl 0.9%, SIAD=syndrome of inappropriate antidiuresis
Table 4. Etiology and Treatment of Hyponatremia for Patients with Initial Serum Sodium $\geq$115 mEq/L who Experienced Osmotic Demyelination Syndrome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Etiology of Hyponatremia</th>
<th>Treatment of hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al. $^{23}$</td>
<td>Not mentioned by authors</td>
<td>NS at 1 lit over 24 h</td>
</tr>
<tr>
<td>Pradhan et al. $^{17}$</td>
<td>Not mentioned by authors, presumably from low solute intake</td>
<td>NS and salt tablets</td>
</tr>
<tr>
<td>Macmillan et al. $^4$</td>
<td>Not mentioned by authors</td>
<td>Not mentioned by the authors</td>
</tr>
<tr>
<td>Pradhan et al. $^{17}$</td>
<td>Salt restriction, persistent vomiting</td>
<td>NS, salt tablets, discontinuation of thiazide diuretic and enalapril</td>
</tr>
<tr>
<td>Zunga et al. $^{16}$</td>
<td>Not mentioned by authors, presumably from viral gastroenteritis</td>
<td>Only mentions ‘supportive treatment’ without specifics.</td>
</tr>
<tr>
<td>Orakzai et al. $^{38}$</td>
<td>Not mentioned by authors</td>
<td>No specific therapy given</td>
</tr>
<tr>
<td>Jahan et al. $^{39}$</td>
<td>Not mentioned by authors, presumably from non-bloody diarrhea</td>
<td>Free water restriction and ‘gentle’ intravenous fluid repletion with NS</td>
</tr>
<tr>
<td>Davenport et al. $^{21}$</td>
<td>SIAD secondary to pneumonia</td>
<td>NS</td>
</tr>
<tr>
<td>Shah et al. $^3$</td>
<td>Not mentioned by authors</td>
<td>Salt tablets and NS</td>
</tr>
</tbody>
</table>

NS=NaCl 0.9%, SIAD=syndrome of inappropriate antidiuresis
Figure Legends

Figure 1. Osmotic Demyelination Syndrome in Reported Cases Despite Changes in SNa that Adhere to Current Hyponatremia Correction Guidelines.

SNa = serum sodium concentration. Open squares represent patients with initial SNa < 115 mEq/L. Closed triangles represent patients with initial SNa ≥ 115 mEq/L. The dashed lines represent therapeutic limits recommended by current hyponatremia guidelines (12mEq/Lin 24 hours and 18mEq/Lin 48 hours). Koul et al not represented in this figure as changes in SNa at 24 and 48 hours were not reported. Two patients with initial SNa < 115 mEq/L (John et al and Malhotra et al) corrected their SNa by 8 mEq/L and 16 mEq/L at 24 and 48 hours, respectively.

Figure 2. Risk Factors for Osmotic Demyelination Syndrome in Reported Cases Based On Initial Serum Sodium

SNa = serum sodium concentration.
Figure 1. Osmotic Demyelination Syndrome in Reported Cases Despite Changes in SNa that Adhere to Current Hyponatremia Correction Guidelines.
Figure 2. Risk Factors for Osmotic Demyelination Syndrome in Reported Cases Based On Initial Serum Sodium

- Malnutrition
- Liver disease
- Hypokalemia
- Alcohol use disorder
- SNa ≤ 105 mEq/L

Percentage of Patients in Each Group

- Initial SNa ≥ 115 mEq/L
- Initial SNa < 115 mEq/L