Risk Factors and Outcomes of Rapid Correction of Severe Hyponatremia

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Abstract

Background and objectives Rapid correction of severe hyponatremia can result in serious neurologic complications, including osmotic demyelination. Few data exist on incidence and risk factors of rapid correction or osmotic demyelination.

Design, setting, participants, & measurements In a retrospective cohort of 1490 patients admitted with serum sodium <120 mEq/L to seven hospitals in the Geisinger Health System from 2001 to 2017, we examined the incidence and risk factors of rapid correction and osmotic demyelination. Rapid correction was defined as serum sodium increase of >8 mEq/L at 24 hours. Osmotic demyelination was determined by manual chart review of all available brain magnetic resonance imaging reports.

Results Mean age was 66 years old (SD=15), 55% were women, and 67% had prior hyponatremia (last outpatient sodium <135 mEq/L). Median change in serum sodium at 24 hours was 6.8 mEq/L (interquartile range, 3.4–10.2), and 606 patients (41%) had rapid correction at 24 hours. Younger age, being a woman, schizophrenia, lower Charlson comorbidity index, lower presentation serum sodium, and urine sodium <30 mEq/L were associated with greater risk of rapid correction. Prior hyponatremia, outpatient aldosterone antagonist use, and treatment at an academic center were associated with lower risk of rapid correction. A total of 295 (20%) patients underwent brain magnetic resonance imaging on or after admission, with nine (0.6%) patients showing radiologic evidence of osmotic demyelination. Eight (0.5%) patients had incident osmotic demyelination, of whom five (63%) had beer potomania, five (63%) had hypokalemia, and seven (88%) had sodium increase >8 mEq/L over a 24-hour period before magnetic resonance imaging. Five patients with osmotic demyelination had apparent neurologic recovery.

Conclusions Among patients presenting with severe hyponatremia, rapid correction occurred in 41%; nearly all patients with incident osmotic demyelination had a documented episode of rapid correction.

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Introduction

Hyponatremia is one of the most common electrolyte disturbances, occurring in approximately 14%–42% of hospitalized patients, and it is associated with higher mortality (1,2). Although the higher risk of death associated with hyponatremia may reflect severity of related illnesses (*e.g.*, congestive heart failure, cirrhosis, and malignancy), acute or severe hyponatremia can result in life-threatening cerebral edema (3). Among patients admitted with severe hyponatremia (sodium <120 mEq/L), in-hospital mortality ranges from 6% to 10% (3,4). Raising serum sodium by 4–6 mEq/L is sufficient to resolve cerebral edema; however, overly rapid correction of severe hyponatremia can result in osmotic demyelination syndrome and central pontine myelinolysis (4–6). Manifestations of osmotic demyelination syndrome can include encephalopathy, seizures, Parkinsonian-like movement disorders, and locked-in syndrome (7–9).

Recent United States guidelines recommend that correction rates not exceed 8 mEq/L for any 24-hour period in patients at high risk for osmotic demyelination (serum sodium ≤105 mEq/L, hypokalemia, malnutrition, or liver disease). European guidelines suggest limiting correction to ≤10 mEq/L in the first 24 hours and ≤8 mEq/L for any 24-hour period thereafter (10–12). Few studies have primarily examined risk factors of overly rapid correction or osmotic demyelination and have been limited by relatively small sample size, limited imaging data, and/or single centers (4,13,14). Reports of osmotic demyelination have mostly been limited to patient reports and small studies (7,15,16). Thus, it remains unclear how often rapid correction or osmotic demyelination occurs in patients presenting with severe hyponatremia.

Using data from seven hospitals in the Geisinger Health System, we examined incidence and risk factors of rapid correction and osmotic demyelination among patients presenting with severe hyponatremia. Our goal was to identify risk factors on the day of admission for rapid correction and osmotic demyelination, enabling clinicians to recognize high-risk patients and potentially prevent devastating neurologic consequences.

Materials and Methods

Study Design and Setting

We extracted data from seven hospitals (one academic and six nonacademic) in the Geisinger Health System, a fully integrated health care system serving central and northeastern Pennsylvania. We included adults ≥18 years of age admitted between January 1, 2001 and February 22, 2017 with an initial serum sodium <120 mEq/L. We excluded patients who had no serum sodium values within 12 hours of the 24- or 48-hour time points after admission and those with serum glucose >300 mg/dl on admission. The Geisinger Institutional Review Board reviewed and approved the research study.

Definition of Rapid Correction Outcomes

Serum sodium and other electrolytes were measured using an indirect ion-selective electrode method (Cobas; Roche Diagnostics). For each study participant, we calculated the estimated serum sodium at 24 hours [Na (24)] using the following formula: Na (24)= $Na^a + [(Na^b - Na^a) \times (24 - T^a)/T^b - T^a)]$, where Na^a and T^a are the closest serum sodium and time values before the 24-hour mark, respectively, and Na^b and T^b are the closest serum sodium and time values after the 24-hour mark, respectively (13). For patients with only one serum sodium value within 12 hours of the 24-hour mark, we used the following formula to estimate serum Na (24): Na (24)= $[(Na^a - Na^0)/T^a] \times 24 + Na^0$ or Na (24)= $[(Na^b - Na^0)/T^b] \times 24 + Na^0$ depending on whether Na^a or Na^b was available.

The primary outcome was rapid correction at 24 hours, which was defined as the estimated rate of serum sodium correction >8 mEq/L at 24 hours. Secondary outcomes included alternative definitions of rapid correction: correction >8 mEq/L at any point during the first 24 hours, correction >10 mEq/L at 24 hours, or correction >18 mEq/L at 48 hours.

Definition of Osmotic Demyelination Syndrome Outcomes

To determine incidence of osmotic demyelination in the study population, we conducted chart reviews on patients with International Classification of Disease (ICD) 9 and 10 diagnostic codes or magnetic resonance imaging (MRI) of the brain at any time after the index serum sodium. MRI reports were manually reviewed by a nephrology fellow by searching for terms such as central pontine myelinolysis, central pontine gliosis, acute osmotic demyelination, and osmotic demyelination syndrome. A nephrology fellow and two attending nephrologists reviewed all charts with MRI evidence of osmotic demyelination to abstract additional details about presentation, hospital course, and outcome.

Other Variables of Interest

Additional data collected included demographics, comorbid conditions by ICD-9/10 codes (cirrhosis, chronic liver disease, nonalcoholic steatohepatitis, hepatic steatosis, fatty liver, alcohol abuse, malnutrition, central pontine myelinolysis, CKD, congestive heart failure, diabetes mellitus, depression, bipolar disorder, and schizophrenia), medications (thiazide and loop diuretics, aldosterone antagonists, selective serotonin reuptake inhibitors, 0.9% normal saline solution, 3% saline solution, vasopressin receptor antagonists, and intravenous or oral electrolyte repletion during admission, including potassium, magnesium, calcium, and phosphorus), clinical data (height, weight, and systolic and diastolic BP measurements), laboratory data on the day of admission (serum sodium, creatinine, potassium, phosphorus, serum osmolality, albumin, urinalysis, urine sodium, urine potassium, and urine osmolality), last outpatient serum sodium value <135 mEq/L, intensive care unit (ICU) stay during admission, and 30-day mortality.

Statistical Analyses

We examined differences between patients who did or did not experience correction >8 mEq/L at 24 hours using nonparametric Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables. The final models for estimation of adjusted odds ratios (aORs) were developed on the basis of clinical rationale and forward selection using Akaike Information Criterion. Because urine sodium was not measured on all patients and inpatient management strategies were likely on the basis of characteristics assessed on presentation, we constructed three multivariable models: (*1*) model 1 included all significant unadjusted risk factors of rapid correction except for urine sodium or inpatient treatment factors, (*2*) model 2 included model 1 covariates and urine sodium (<30 or ≥30 mEq/L), and (*3*) model 3 included model 1 covariates and inpatient treatment factors. A P value of <0.05 was considered statistically significant for all comparisons without adjustment for multiple comparisons.

Results

Study Cohort Characteristics

A total of 1718 patients were admitted between January 1, 2001 and February 22, 2017 with severe hyponatremia on admission (sodium <120 mEq/L). After excluding 42 patients missing serum sodium values within 12 hours of the 24- or 48-hour time points after admission and 186 patients who had plasma glucose >300 mg/dl on admission, 1490 patients were included in the main analysis. The baseline characteristics are shown in Table 1. Median (interquartile range [IQR]) change in serum sodium was 6.8 mEq/L (IQR, 3.4–10.2) at 24 hours and 10.3 mEq/L (IQR, 6.5–14.8) at 48 hours (Figure 1). A total of 606 (41%) and 390 (26%) patients had correction >8 mEq/L and correction >10 mEq/L at 24 hours, respectively; 166 (12%) of 1346 patients with 48-hour sodium data had correction >18 mEq/L at 48 hours.

Patients who experienced correction >8 mEq/L at 24 hours were more likely to be younger (63 versus 68 years old), be current smokers (40% versus 26%), have lower body mass index (26 versus 28 kg/m^2), have a history of depression (20% versus 16%), have schizophrenia (4% versus 1%), and have seizures (13% versus 9%), and they were less likely to have prior hyponatremia (59% versus 73%), chronic liver disease (6% versus 8%), congestive heart failure (12% versus 19%), or cancer (19% versus 25%). Rapid correctors had lower mean values for initial serum sodium (115 versus 117 mEq/L), random urine sodium (35 versus 43 mEq/L), urine potassium (27 versus 32 mEq/L), and urine osmolality (270 versus 369 mOsm/kg).

Table 1. Characteristics of adults admitted to Geisinger system hospitals with an initial serum sodium <120 mEq/L by change in serum sodium at 24 hours after admission

Characteristic	Na^+ Correction of ≤8 mEq/L at 24 h, *n*=884	Na^+ Correction of >8 mEq/L at 24 h, *n*=606
Age, yr	68 (15)	63 (15)
Women, *n* (%)	460 (52)	359 (59)
Non-Hispanic white	865 (98)	594 (98)
Smoking status, *n* (%)		
Current smoker	216 (26)	225 (40)
Former smoker	287 (35)	138 (24)
Never smoker	310 (37)	186 (33)
Unknown	18 (2)	18 (3)
Body mass index, kg/m^2	28 (8)	26 (6)
Systolic BP, mm Hg	133 (29)	136 (30)
Diastolic BP, mm Hg	71 (17)	74 (18)
Comorbidities, *n* (%)		
Chronic liver disease	72 (8)	36 (6)
CKD	109 (12)	57 (9)
Nonalcoholic steatohepatits	13 (2)	11 (2)
Hepatic steatosis	30 (3)	27 (5)
Fatty liver	66 (8)	35 (6)
Alcohol abuse	140 (16)	122 (20)
Malnutrition	304 (34)	202 (33)
Congestive heart failure	164 (19)	73 (12)
Diabetes mellitus	145 (16)	83 (14)
Depression	141 (16)	123 (20)
Bipolar disorder	41 (5)	37 (6)
Schizophrenia	12 (1)	22 (4)
Epilepsy	83 (9)	79 (13)
Seizure	81 (9)	80 (13)
Stroke	49 (6)	32 (5)
Dementia	9 (1)	6 (1)
Cancer	218 (25)	115 (19)
Charlson, *n* (%) comorbidity index		
0	26 (3)	45 (7)
1	46 (5)	60 (10)
2	80 (9)	86 (14)
≥3	732 (83)	415 (69)
ICU stay during the first 24 h after hospital admission, *n* (%)	187 (21)	129 (21)
Outpatient Na^+ value <135 mEq/L, *n* (%)	528 (73)	294 (59)
Admission laboratory values		
Sodium, mEq/L, *n*=1490	117 (4)	115 (5)
Creatinine, mg/dl, *n*=1452	1.3 (1.5)	1.3 (2.0)
eGFR, ml/min/1.73m^2, *n*=1452	72 (35)	80 (36)
Potassium, mEq/L, *n*=1489	4.3 (1.0)	4.0 (1.0)
Phosphorus, mg/dL, *n*=851	3.5 (1.9)	3.3 (2.0)
Magnesium, mg/dL, *n*=927	1.9 (0.4)	1.8 (0.4)
Osmolality, mOsm/kg, *n*=951	263 (94)	258 (19)
Albumin, g/dL, *n*=1280	3.3 (0.7)	3.6 (0.6)
Glucose, mg/dL, *n*=1489	127 (40)	128 (40)
Urine sodium, mEq/L, *n*=1141	43 (38)	35 (31)
Urine potassium, mEq/L, *n*=421	32 (17)	27 (19)
Urine osmolality, mOsm/kg, *n*=1083	369 (150)	270 (149)
Outpatient medications, *n* (%)		
Thiazide diuretics	64 (7)	36 (6)
Loop diuretics	226 (26)	76 (13)
Aldosterone antagonists	102 (12)	25 (4)
Selective serotonin reuptake inhibitors	150 (17)	113 (19)
Antiseizure medications	154 (17)	121 (20)
Antipsychotic medications	98 (11)	92 (15)
Inpatient medications, *n* (%)		
Hypertonic saline	82 (9)	104 (17)
Electrolyte repletion	240 (27)	236 (39)
Vaptans	11 (1)	7 (1)
Mortality within 30 d of hospital admission, *n* (%)	167 (19)	46 (8)

Values are presented as mean (SD) or number (%). ICU, intensive care unit; Na^+, sodium.

Risk Factors of Rapid Correction at 24 Hours

In multivariable analyses not including urine sodium or inpatient treatment factors (model 1), being a woman was associated with higher risk of rapid correction at 24 hours (aOR, 1.49; 95% confidence interval [95% CI], 1.14 to 1.96), whereas treatment at an academic medical center (aOR, 0.70; 95% CI, 0.54 to 0.90), higher Charlson comorbidity index (aOR, 0.94; 95% CI, 0.89 to 0.99), older age (aOR, 0.98; 95% CI, 0.97 to 0.99), prior hyponatremia (aOR, 0.62; 95% CI, 0.48 to 0.81), higher baseline serum sodium at hospitalization (per 1-mEq/L higher serum sodium; aOR, 0.90; 95% CI, 0.87 to 0.93), and outpatient aldosterone antagonist use (aOR, 0.48; 95% CI, 0.28 to 0.82) were associated with lower risk of rapid correction at 24 hours (Table 2). In multivariable analyses including urine sodium (model 2), urine sodium <30 mEq/L was significantly associated with greater risk of rapid correction at 24 hours (aOR, 1.58; 95% CI, 1.17 to 2.13); other results were largely unchanged. In multivariable analyses including urine sodium and inpatient treatment factors (model 3), none of the inpatient treatment factors (electrolyte repletion, vaptan, or ICU stay) were associated with risk of rapid correction at 24 hours.

In sensitivity analyses using different definitions of rapid correction (>10 mEq/L at 24 hours, >18 mEq/L at 48 hours, or >8 mEq/L from baseline to any point during the initial 24 hours), results were largely consistent with a few exceptions (Supplemental Tables 1–3). Vaptan use was associated with higher risk (aOR, 3.92; 95% CI, 1.09 to 14.09) and ICU stay was associated with lower risk (aOR, 0.54; 95% CI, 0.31 to 0.96) of rapid correction >18 mEq/L at 48 hours. Treatment at an academic center was not associated with greater risk of correction >8 mEq/L from

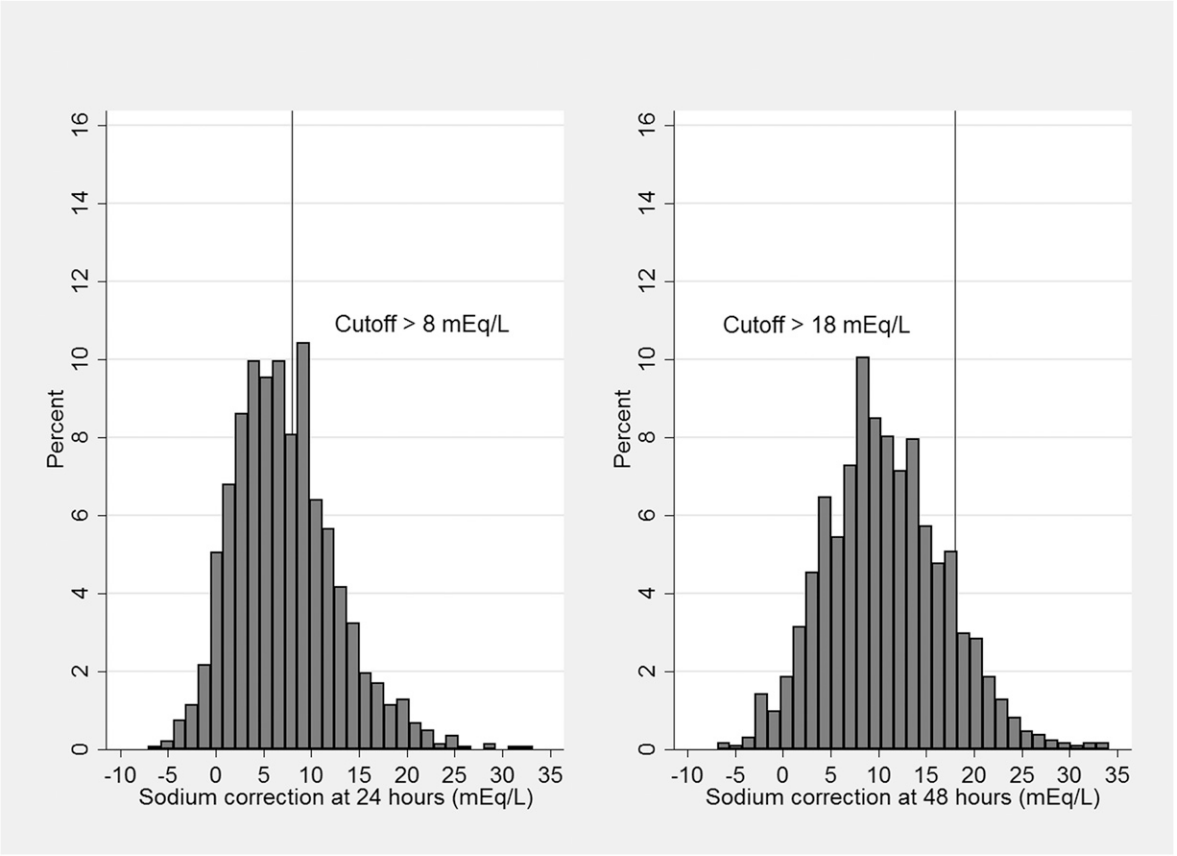

Figure 1. | Distribution of sodium correction from baseline to 24 and 48 hours and degree of sodium rise above cutoff level in patients admitted to Geisinger with initial serum sodium <120 mEq/L.

baseline to any point during the initial 24 hours (aOR, 1.03; 95% CI, 0.78 to 1.36).

Incidence and Risk Factors of Osmotic Demyelination

A total of 295 (20%) patients had brain MRI completed during follow-up, with nine patients (0.6%) showing radiologic evidence of osmotic demyelination; no patients had ICD diagnoses of central pontine myelinolysis. One patient already had osmotic demyelination on admission MRI. Patient characteristics, risk factors, sodium trends, treatments, and outcomes are shown in Figure 2 and Table 3. Of the eight (0.5%) patients who developed incident osmotic demyelination, seven (88%) had documented sodium correction >8 mEq/L during any 24-hour period before brain MRI. The one patient without documented evidence of rapid correction was noted to have serum sodium levels of 105 and 132 mEq/L in the month before index admission, but further details on timing were lacking. Important characteristics observed in the patients with incident osmotic demyelination included hypovolemia (75%), beer potomania (63%), outpatient thiazide diuretic use (25%), alcohol use disorder (50%), malnutrition (50%), and hypokalemia (63%). Three patients received 3% saline before rapid correction due to acute neurologic symptoms. Dextrose 5% water solution was given to three patients and desmopressin was given to one patient to slow the rate of sodium correction. Five patients with documented osmotic demyelination had recovery with no neurologic deficits, two patients died from unrelated causes, and two were lost to follow-up.

Discussion

In a large cohort of patients presenting with severe hyponatremia, we examined clinical and radiologic data to describe incidence and risk factors of rapid correction and osmotic demyelination. We found that 41% of patients experienced correction >8 mEq/L at 24 hours, that 12% had correction >18 mEq/L at 48 hours, and that 0.5% of patients had incident osmotic demyelination confirmed by MRI. We found a significant number of risk factors of rapid correction and osmotic demyelination, confirming previously described associations and identifying some novel risk factors. Risk was more than twofold higher among patients with schizophrenia, although none of the 22 patients with schizophrenia who rapidly corrected developed osmotic demyelination. Because primary polydipsia is common in patients with schizophrenia, it seems likely that hyponatremia may have developed acutely in these patients from water intoxication before chronic hyponatremia brain cell adaptation occurred (17). Patients who presented at an academic center had a 30% lower risk of rapid correction >8 mEq/L at 24 hours and a 61% lower risk of rapid correction >18 mEq/L at 48 hours. This suggests that improved, timely access to specialists, such as nephrologists or

Table 2. Factors associated with sodium correction >8 mEq/L at 24 hours in patients admitted to Geisinger system hospitals with an initial serum sodium <120 mEq/L

Variables	OR (95% CI)			
	Unadjusted	Model 1	Model 2	Model 3
Academic center	0.65 (0.53 to 0.81)[a]	0.70 (0.54 to 0.90)[a]	0.70 (0.52 to 0.94)[b]	0.70 (0.54 to 0.91)[a]
Women	1.34 (1.08 to 1.65)[a]	1.49 (1.14 to 1.96)[a]	1.73 (1.26 to 2.37)[a]	1.50 (1.14 to 1.96)[a]
Age, per 1 yr	0.98 (0.97 to 0.99)[a]	0.98 (0.97 to 0.99)[a]	0.98 (0.97 to 0.99)[a]	0.98 (0.97 to 0.99)[a]
White	1.03 (0.49 to 2.15)	1.03 (0.37 to 2.92)	0.74 (0.23 to 2.35)	1.01 (0.36 to 2.88)
Schizophrenia	2.73 (1.34 to 5.57)[a]	2.24 (1.03 to 4.89)[b]	2.48 (1.02 to 6.02)[b]	2.24 (1.03 to 4.88)[b]
Congestive heart failure	0.60 (0.45 to 0.81)[a]	0.94 (0.66 to 1.33)	1.08 (0.72 to 1.63)	0.94 (0.67 to 1.34)
Charlson comorbidity index	0.86 (0.82 to 0.89)[a]	0.94 (0.89 to 0.99)[b]	0.93 (0.87 to 0.99)[b]	0.94 (0.88 to 0.99)[b]
Outpatient Na^+ <135	0.52 (0.41 to 0.67)[a]	0.62 (0.48 to 0.81)[a]	0.62 (0.46 to 0.84)[a]	0.62 (0.48 to 0.81)[a]
Inpatient baseline Na^+ at hospitalization	0.88 (0.86 to 0.91)[a]	0.90 (0.87 to 0.93)[a]	0.90 (0.87 to 0.93)[a]	0.90 (0.87 to 0.93)[a]
Urine Na^+ <30 mEq/L	1.46 (1.15 to 1.85)[a]		1.58 (1.17 to 2.13)[a]	
K^+≥5 mEq/L	0.87 (0.66 to 1.16)	1.22 (0.88 to 1.71)	1.14 (0.76 to 1.70)	1.23 (0.87 to 1.74)
K^+<3.5 mEq/L	1.81 (1.41 to 2.33)[a]	1.32 (0.97 to 1.79)	1.39 (0.97 to 1.97)	1.24 (0.88 to 1.73)
Loop diuretics (outpatient)	0.42 (0.31 to 0.56)[a]	0.71 (0.49 to 1.02)	0.66 (0.43 to 1.01)	0.71 (0.49 to 1.02)
Aldosterone antagonists (outpatient)	0.33 (0.21 to 0.52)[a]	0.48 (0.28 to 0.82)[a]	0.45 (0.23 to 0.84)[b]	0.48 (0.28 to 0.83)[a]
Hypertonic saline (inpatient)	2.03 (1.49 to 2.76)[a]			1.09 (0.73 to 1.64)
Electrolyte repletion (inpatient)	1.71 (1.37 to 2.13[a]			1.14 (0.84 to 1.55)
Vaptans (inpatient)	0.93 (0.36 to 2.41)			1.21 (0.40 to 3.63)
ICU stay in the first 24 h after admission	1.01 (0.78 to 1.30)			1.07 (0.79 to 1.44)

Model 1 included all significant unadjusted risk factors of rapid correction except for urine sodium or inpatient treatment factors. Model 2 included model 1 covariates and urine sodium (<30 or ≥30 mEq/L). Model 3 included model 1 covariates and inpatient treatment factors. OR, odds ratio; 95% CI, 95% confidence interval; Na^+, sodium; K^+, potassium; ICU, intensive care unit.
[a]Significant at P=0.01.
[b]Significant at P=0.05.

intensivists, may be helpful in managing patients presenting with severe hyponatremia, although carefully designed, prospective studies are needed to show this.

To our knowledge, our cohort is the largest to examine the prevalence of MRI-confirmed osmotic demyelination in patients presenting with severe hyponatremia. A prospective imaging study investigating neurologic outcomes using serial brain MRI in 13 patients with severe hyponatremia (serum sodium <115 mEq/L) found osmotic demyelination lesions in three patients, all of whom had a serum sodium increase well beyond 8 mEq/L at 24 hours (mean of 30 mEq/L per day) (18). In other retrospective studies of patients who were severely hyponatremic, osmotic demyelination occurred in 0.2%–2% of patients (4,13). In our study, we examined all brain MRI reports completed on patients presenting with severe hyponatremia. Interestingly, despite a 41% incidence of rapid correction, only eight patients experienced incident osmotic demyelination during hospitalization, and one presented with osmotic demyelination syndrome, which was confirmed by MRI on admission day. Seven of eight patients with incident osmotic demyelination experienced sodium correction >8 mEq/L over any 24-hour period before brain MRI, and one possibly had rapid correction during admission at an outside hospital. Consistent with other patient series, we observed considerable heterogeneity in neurologic symptoms ranging from encephalopathy to persistent seizures or primarily cerebellar symptoms (19). Of the six alcoholic patients who had osmotic demyelination, two were lost to follow-up, and four surprisingly had recovery of neurologic function according to follow-up chart documentation, with two of four maintaining long-term sobriety. Interestingly, long-term neurologic outcomes in our cohort seemed better than those of other prior reports (19,20). This could be, in part, due to differences in study design and cohort selection.

Our findings suggest an association between rapid correction and osmotic demyelination, consistent with experimental animal models and some but not all observational

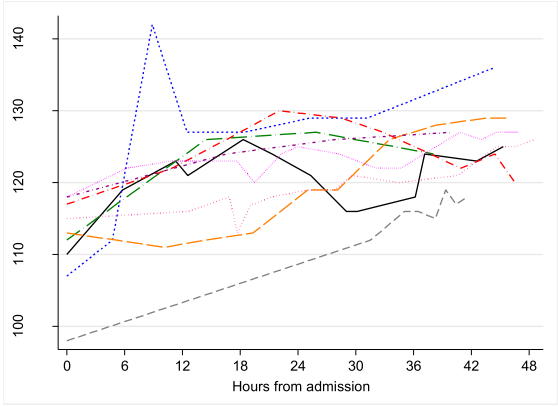

Figure 2. | Serum sodium trends during the first 24 and 48 hours of admission in patients with radiologic evidence of osmotic demyelination.

Table 3. Characteristics of patients admitted to Geisinger system hospitals with an initial serum sodium <120 mEq/L and osmotic demyelination on magnetic resonance imaging

Patient	Hospital	Initial Serum; Urine Sodium, mEq/L	Hyponatremia Etiology	Osmotic Demyelination Risk Factors	Initial Treatment	Urine Output over the First 24 h, ml
Patients with incident osmotic demyelination occurring after admission						
Patient 1: 39-yr-old man with alcoholism, presented with pneumonia and encephalopathy	Academic center	Serum 110; urine 46[a]	Hypovolemia, beer potomania	Hypokalemia, alcohol use disorder, malnutrition	3% Saline	3900
Patient 2: 52-yr-old woman with alcoholism, HTN, depression on sertraline presented with lethargy	Transfer from OSH to academic center	Serum 98; urine 25	Hypovolemia, beer potomania, thiazide	Hypokalemia, malnutrition, alcohol use disorder	0.9% Saline	Not documented
Patient 3: 52-yr-old woman with alcoholism, depression on mirtazapine presented with seizures and hypotension	Nonacademic hospital	Serum 107; urine 52[a]	Hypovolemia, beer potomania	Alcohol use disorder	3% Saline, 0.9% saline	4300
Patient 4: 58-yr-old woman with alcoholism, spinal stenosis, HTN, prior hyponatremia on salt tablets presented with seizure, inebriation	Nonacademic hospital	Serum 112; urine 114[c]	Beer potomania, thiazide	Alcohol use disorder	0.9% Saline	1100 in an 8-h period, then not documented
Patient 5: 38-yr-old man with alcoholism, HTN on thiazide, depression on fluoxetine presented with unsteadiness and acute pancreatitis	Nonacademic hospital	Serum 113	Hypovolemia, beer potomania	Hypokalemia, alcohol use disorder	0.9% Saline	2300
Patient 6: 59-yr-old woman with multiple sclerosis, RA, HTN on thiazide, bipolar disorder on quetiapine and mirtazapine presented with encephalopathy, hypotension, and blurred vision	Academic center	Serum 117; urine <20	Hypovolemia, thiazide	Hypokalemia, malnutrition	0.9% Saline	3690
Patient 7: 36-yr-old woman with alcoholism presented with shortness of breath, severe anemia	Transfer from OSH to academic center	Serum 115; urine <10	Hypervolemic	Hypokalemia, malnutrition, alcohol use disorder, end stage liver disease (MELD score 29)	0.9% Saline, 3% saline	515
Patient 8: 69-yr-old woman with diffuse large B cell lymphoma, prior hyponatremia presented with shortness of breath, malignant pleural effusion	Academic center	Serum 118	Hypovolemia	Prior hyponatremia	0.9% Saline	175
Patient with osmotic demyelination occurring before hospitalization with severe hyponatremia						
Patient 9: 32-yr-old man with depression, heavy alcohol use presented with 5 d of dysarthria and ataxia; also reported salt craving and high salt intake in the 2 wk before presentation	Transfer from OSH to academic center	Serum 118; urine <10	Hypovolemia, beer potomania	Hypokalemia, alcohol use disorder, malnutrition	0.9% Saline	977

MRI, magnetic resonance imaging; Na^+, sodium; D5W, dextrose 5% in water; HTN, hypertension; OSH, outside hospital; RA, rheumatoid arthritis; MELD, model for end stage liver disease.
[a]Checked after receiving 3% saline.
[b]Per follow-up progress notes.
[c]On salt tablets as outpatient.

Table 3. Continued

Correction >8 mEq/L before MRI (Maximum over 24 h); Actions taken to Slow Rise	Neurologic Signs before MRI	Nephrology Consult	Timing of MRI after Initial Na^+	Site(s) Involved	Outcome
Yes (12 mEq/L), on day 1; D5W given	Upper extremity spasticity, mutism, encephalopathy	Yes	18 d later	Central pons	Wheelchair bound 1 yr, no neurologic deficits at 4 yr[b]; alcohol cessation
Yes (11 mEq/L), on day 1; D5W given	Hyper-reflexia, ataxia, bilateral lower extremity weakness, confusion	Yes	7 d later	Central pons	No neurologic deficits at 3 mo[b]; alcohol cessation
Yes (22 mEq/L), on day 1	Lower extremity hyporeflexia, recurrent seizures	No	3 d later	Central pons	No neurologic deficits at 2 yr[b]; ongoing alcohol abuse
Yes (15 mEq/L), on day 1	Ataxia, lower extremity hyporeflexia, seizure	Yes	14 mo later	Central pons	Gait dysfunction, recurrent episodes of severe hyponatremia and alcohol intoxication; died 4 yr later from sepsis and hepatic encephalopathy
Yes (16 mEq/L), on day 2	Decreased visual acuity, hyper-reflexia, ataxia	No	11 d later	Central pons, bilateral frontal, parieto-occipital, cerebellum, basal ganglia, and external capsules	No neurologic deficits at 6 mo[b]; ongoing alcohol abuse
Yes (13 mEq/L), on day 1; D5W, desmopressin	Aphasia, lower extremity weakness	Yes	124 d later	Central pons, bilateral cerebral white matter, not seen on prior MRI before rapid correction	Death at 1 yr from septic shock due to clostridium difficile colitis
Yes (9 mEq/L), on day 3	Seizure, generalized weakness	Yes	18 d later	Central pons, bilateral thalamus, subinsular regions	Lost to follow-up
No (7 mEq/L) but sodium 105 and 132 mEq/L in prior month at OSH without documentation of timing	Encephalopathy, seizure	No	14 d later	Central pons, bilateral basal ganglia	No neurologic deficits[b]
No (7 mEq/L); D5W[c]	Ataxia, dysarthria, dysmetria, intention tremor, opsoclonus	Yes	<24 h later	Central pons, cerebellum	Lost to follow-up

studies (16,18,21–23). We found that further chart review was required to ascertain rapid correction in some patients with incident osmotic demyelination, because outpatient serum sodium values from outside hospitals were available in some progress notes, and two patients had sodium correction >8 mEq/L over a 24-hour period after day 1. Osmotic demyelination can also occur in other settings, such as hyperosmolar hyperglycemia, hyperammonemia, hypoxia, severe liver disease, and chronic alcoholism, in the absence of documented rapid sodium correction (24–29). The exact mechanism of demyelination in the setting of alcohol abuse is not entirely clear but could be related to direct neurotoxicity of alcohol, malnutrition, or underlying liver disease (26).

In our cohort, common features among patients who developed osmotic demyelination included hypovolemia, beer potomania, malnutrition, and hypokalemia. Commonly,

patients who are hypovolemic are treated with normal saline boluses in the emergency department, often empirically on the basis of clinical assessment of fluid status. Although correction of hypovolemia is essential for stabilization of fluid status and hemodynamics, such patients are at risk for brisk water diuresis on correction of their hypovolemia, which can then lead to rapid sodium correction and the potentially catastrophic effects of osmotic demyelination. Hypokalemia was common on presentation in patients with incident osmotic demyelination, similar to other studies (15,16,30). We also found that a random urine sodium <30 mEq/L was associated with higher risk of rapid correction. This directly correlates with previous findings that a urine sodium of <30 mEq/L is superior to clinical assessment of volume status in identifying hyponatremic patients who would correct with isotonic saline administration (4,31). However, in edematous states, such as heart failure or cirrhosis, urine sodium may not be useful to assess risk of rapid correction, because a low value could reflect a state of decreased effective arterial blood volume in the setting of diminished cardiac output or systemic vasodilation. We also found that most patients who developed osmotic demyelination received 0.9% saline rather than 3% saline empirically on the basis of clinical assessment of hypovolemia. These findings emphasize the importance of thoughtful initial fluid management of patients who are severely hyponatremic, being mindful of potential risk of rapid correction when euvolemia is restored.

Treatment of severe hyponatremia with hypertonic saline is necessary and indicated for patients who present with severe neurologic symptoms (32). Previous uncontrolled studies have suggested that, when used in a specific, regimented protocol, hypertonic saline can be safe and effective in reversing the symptoms of hyponatremic encephalopathy (32–34). However, the effect of hypertonic saline dosing on serum sodium increase can be unpredictable, even with use of traditional formulas for dose calculation (30). Other strategies, such as combined administration of desmopressin and 3% saline, have been suggested to raise serum sodium in a controlled fashion (35). Further studies are needed to determine optimal initial management strategies for severe hyponatremia. Reversing rapid correction of hyponatremia with desmopressin and/or hypotonic fluids in osmotic demyelination animal models has been shown to reduce mortality, but data in humans are limited (36).

Our study has several strengths and limitations. Major strengths include the large number of patients in the cohort with data on rapid correction and osmotic demyelination as defined by manual review of every brain MRI report after initial hospitalization for severe hyponatremia and selected chart review for those with radiologic evidence of osmotic demyelination. The results should be interpreted cautiously given the study's retrospective design and our inability to conduct chart review on the entire cohort to determine etiology of hyponatremia. We did not have complete laboratory data (such as urine sodium) on all patients, and we did not quantify exact doses of electrolyte repletion. Although the Geisinger Health System includes most hospitals in its coverage area, some patients were transferred from outside hospitals and may have lacked data on serum sodium values or signs of osmotic demyelination before transfer. Our study population was limited to mostly white patients in central and northeast Pennsylvania, although we included data from six nonacademic hospitals and one academic center. We only assessed risk factors within the first 24 hours of admission and did not examine rapid correction that may have occurred during the later periods of hospitalization for all patients. As noted in our study, ICD codes have poor sensitivity for osmotic demyelination, and we may have missed patients with osmotic demyelination who did not undergo brain MRI. Therefore, the incidence of rapid correction of severe hyponatremia and osmotic demyelination may have been underestimated in our cohort. Further research with blinded evaluation of brain MRIs in patients with severe hyponatremia may be needed to detect patients with more subtle cases of osmotic demyelination.

In conclusion, sodium correction >8 mEq/L at 24 hours occurred in 41% of patients presenting with severe hyponatremia in a large integrated health system. Risk factors of rapid correction included being a woman, younger age, history of schizophrenia, lower initial serum sodium value, and urine sodium <30 mEq/L. Hypovolemia, beer potomania, malnutrition, and hypokalemia were common in patients presenting with severe hyponatremia who developed incident osmotic demyelination. Future efforts are needed to identify optimal strategies for reducing risk of rapid correction and osmotic demyelination in patients presenting with severe hyponatremia.

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Disclosures

None.

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