Research Square

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Osmotic demyelination syndrome in severe hyponatremia: independent association with sodium correction rates when accounting for established risk factors.

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Abstract

Introduction:

Clinical guidelines emphasize slow correction of severe hyponatremia to prevent osmotic demyelination syndrome (ODS), but there is sparse data on relative impact of ODS risk factors.

Methods

Retrospective cohort study of adults with an initial serum sodium concentration ≤ 120 meq/L admitted to a 21-hospital integrated healthcare system between January 1, 2008 to December 31, 2023. Maximum 24-hour sodium correction was defined as slow (< 6 meq/L), moderate (8–12 meq/L) or fast (> 12 meq/L). Adjusted odds ratios (aOR) were determined using Firth's penalized logistic regression.

Results

Of 16,021 patients, 23 (0.14%) cases of ODS were identified. Compared to ODS cases had lower initial serum sodium (112 vs 117 meq/L) and were more likely to have a major ODS risk factor (70% vs 23%) and undergo fast sodium correction (43% vs 24%). Initial serum sodium ≤ 105 meq/L (aOR 10.3, 95% CI 3.3 to 32.3), initial serum potassium < 3.0 meq/L (aOR 3.4, 95% CI 1.2 to 9.3), and history of alcohol abuse (aOR 3.9, 95% CI 1.7 to 8.8) were independently associated with ODS; the maximum rate of sodium correction was not.

Conclusion

Baseline risk factors are far more deterministic of ODS than marginal differences in sodium correction rates.

Introduction

Severe hyponatremia, defined as a serum sodium concentration below 12 mmol/L, has a prevalence of approximately 1% among hospital inpatients and is associated with substantial morbidity and mortality.[1] Clinical practice guidelines emphasize slow and controlled correction of severe hyponatremia to avoid potentially devastating neurologic damage from osmotic demyelination syndrome (ODS, formerly termed central pontine myelinolysis), with recommended sodium correction targets as slow as 4 to 6 meq/L per 24 hours in patients with risk factors for ODS.[2,3] While animal and observational evidence suggest that very fast sodium correction (e.g. > 25 meq/L per 24 hours) can result in ODS, the relative risks at lower thresholds are less certain.[4] A recent meta-analysis examining associations between ODS and sodium correction rates among patients with severe hyponatremia reported no significant risk difference when

comparing fast (≥ 8–10 meq/L per 24 hours) with slow (< 8 or 6–10 mEq/L per 24 hours) or very slow (< 4–6 mEq/L per 24 hours) correction, though fast correction did have a higher unadjusted odds of ODS in sensitivity analyses (Peto odds ratio, 2.34; 95% CI, 1.01–5.46 and 4.03; 95% CI, 1.13–14.41, respectively).[5] Separate meta-analyses likewise reported varying confidence around the unadjusted association between fast sodium correction and ODS or neurologic events, specifically when restricted to higher-quality studies.[6,7] Since adjustment for confounding factors has been precluded by small event numbers in individual studies, we sought to assemble a large case-control cohort to assess whether the association between fast correction and ODS persisted when controlling for major ODS risk factors (history of alcohol abuse, initial serum potassium < 3.0 meq/L, or an initial serum sodium ≤ 105 meq/L).[8–10]

Short Methods

We conducted a retrospective cohort study within Kaiser Permanente Northern California (KPNC), an integrated healthcare system with 21 community hospitals serving a diverse patient population, of adult patients (age ≥ 18 years) admitted from the emergency department with an initial serum sodium concentration of ≤ 120 meq/L between January 1, 2008 to December 31, 2023.[11] Cases of possible ODS were identified for manual review and adjudication if there was either: 1) an International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10) coded diagnoses of demyelinating diseases of central nervous system (341.8x/G37.x) within 90 days following hospital admission or 2) brain imaging (computed tomography or magnetic resonance imaging) obtained within 90-days of admission with a final interpretation noting possible demyelination; controls were patients without confirmed ODS who were alive at 90 days following admission. Maximum rates of 24-hour sodium correction were calculated relative to both the initial any subsequent serum sodium measurement below 120 meq/L. Given the low number of ODS outcomes, the association between ODS and varying rates of maximal sodium correction was estimated using Firth's penalized logistic regression with covariate adjustment for each major ODS risk factor noted above, reported as adjusted odds ratios (aOR) with 95% CIs.[12] Further methodologic details are provided in the Supplementary Material.

Results

Of 16,021 unique patients admitted with severe hyponatremia during the study period, there were 23 cases of ODS identified (0.14%; 20 by ICD codes, 3 by imaging review, Table S1) and 9557 controls, as defined in the Supplementary Materials. Patients with ODS were younger (57 vs 72 years), had lower initial serum sodium levels (112 vs 117 meq/L), were more likely to have at least one major ODS risk factor (70% vs 23%), and were more likely to undergo fast serum sodium correction (43% vs 24%, Table 1). In adjusted analysis using penalized logistic regression (Table 2), faster 24-hour rates of sodium correction were not associated with the development of ODS (8–12 meq/L aOR of 0.6, 95% CI 0.2 to 2.0; > 12 meq/L aOR 1.0, 95% CI 0.3 to 2.9). In contrast, each major ODS risk factor was independently associated with the development ODS: initial serum [Na+] ≤ 105 meq/L (aOR 10.3, 95% CI

3.3 to 32.3), initial serum [K+] < 3.0 meq/L (aOR 3.4, 95% CI 1.2 to 9.3), and history of alcohol abuse (aOR 3.9, 95% CI 1.7 to 8.8). Findings were consistent in sensitivity analyses restricted to patients without diabetes (to exclude potential confounding on serum sodium measurements from unmeasured hyperglycemia, 18 cases and 6833 controls, Table 2 and Supplementary Materials) and when matching cases to controls in a 1:3 ratio based on severity of hyponatremia and hypokalemia, age difference less than 20 years, and history of alcohol abuse (Table 3).

Table 1
Characteristics, exposures and maximum 24-hour serum [Na+] correction

N (%)	Case (n = 23)	Control (n = 9557)
Age, median (IQR)	57 (44–65)	72 (64–82)
Female	12 (52)	6196 (65)
Race		
Black	0 (0)	356 (4)
Asian	4 (17)	2244 (23)
Hispanic	1 (4)	1083 (11)
White	18 (78)	5223 (55)
Other/unknown	0 (0)	651 (7)
Liver disease	9 (39)	1504 (16)
Congestive heart failure	4 (17)	2030 (21)
Malnutrition	6 (26)	1044 (11)
Alcohol abuse	10 (43)	1295 (14)
Metastatic cancer	1 (4)	479 (5)
Diuretic	12 (52)	6802 (71)
Antidepressant	6 (26)	1803 (19)
Antipsychotic	1 (4)	700 (7)
Anticonvulsant	3 (13)	1589 (17)
Initial serum [Na+]		
Median (IQR)	112 (105–118)	117 (113–119)
115–120 meq/L	10 (43)	6513 (68)
106–114 meq/L	6 (26)	2752 (29)
≤ 105 meq/L	7 (30)	292 (3)
Initial serum [K+]		
Median (IQR)	3.1 (2.8–4.2)	4.0 (3.5–4.6)
≥ 3.5 meq/L	10 (43)	7306 (76)
3.0-3.4 meq/L	6 (26)	1377 (24)
Abbreviations:		

N (%)	Case (n = 23)	Control (n = 9557)
< 3.0 meq/L	7 (30)	874 (9)
Any major ODS risk factor*	16 (70)	2161 (23)
Exposures		
Initial admission to ICU	12 (52)	2142 (22)
Desmopressin	4 (17)	869 (9)
Dextrose in water	13 (57)	3459 (36)
Hypertonic saline	6 (26)	2323 (24)
Maximum 24-hour [Na+] correction rate (meq/L)		
< 8	8 (35)	4319 (45)
8–12	5 (21)	2971 (31)
> 12	10 (43)	2267 (24)
Abbreviations:		

Table 2
Adjusted odds of developing osmotic demyelination syndrome.

Entire case-control cohort (n = 9580)	**aOR (95% CI)**	**P-value**
Initial serum [Na+]		
115–120 meq/L	Reference	NA
106–114 meq/L	1.3 (0.5–3.8)	0.58
≤ 105 meq/L	10.3 (3.3–32.3)	< 0.001
Initial serum [K+]		
≥ 3.5 meq/L	Reference	NA
3.0-3.4 meq/L	2.5 (0.9–6.9)	0.071
< 3.0 meq/L	3.4 (1.2–9.3)	0.019
History of alcohol abuse	3.9 (1.7–8.8)	0.001
Maximum 24- hour [Na+] correction rate		
< 8 meq/L	Reference	NA
8–12 meq/L	0.6 (0.2–2.0)	0.45
> 12 meq/L	1.0 (0.3–2.9)	0.93
Restricted case-control cohort (excluding patients with diabetes, n = 6581)		
Initial serum [Na+]		
115–120 meq/L	Reference	NA
106–114 meq/L	1.2 (0.4–4.2)	0.72
≤ 105 meq/L	14.9 (4.0–55.6)	< 0.001
Initial serum [K+]		
≥ 3.5 meq/L	Reference	NA
3.0-3.4 meq/L	3.6 (1.1–11.4)	0.032
Abbreviations: aOR = adjusted odds ratio.		
Model estimates generated using Firth's penalized logistic regression. Restricted cohort included 18 cases and 6833 controls without a history of diabetes (to reduce potential confounding by unmeasured hyperglycemia on apparent rates of sodium correction).		

Entire case-control cohort (n = 9580)	aOR (95% CI)	P-value
< 3.0 meq/L	6.3 (2.0–19.2)	0.001
History of alcohol abuse	2.8 (1.1–7.2)	0.032
Maximum 24- hour [Na+] correction rate		
< 8 meq/L	Reference	NA
8–12 meq/L	0.6 (0.2–2.0)	0.42
> 12 meq/L	0.4 (0.1–1.6)	0.21
Abbreviations: aOR = adjusted odds ratio.		
Model estimates generated using Firth's penalized logistic regression. Restricted cohort included 18 cases and 6833 controls without a history of diabetes (to reduce potential confounding by unmeasured hyperglycemia on apparent rates of sodium correction).		

Table 3
Sodium correction rates in the matched case-control cohort.

	Maximum 24-hour rate of [Na+] correction (%)		
	< 8 meq/L	8–12 meq/L	> 12 meq/L
Matched controls (n = 66)	19 (29)	20 (30)	27 (41)
ODS cases (n = 23)	8 (35)	5 (22)	10 (44)
Abbreviations: ODS = osmotic demyelination syndrome.			
Cases with ODS were matched to controls by ODS risk factors (degree of hyponatremia, degree of hypokalemia, and history of alcohol abuse) and age difference less than 20 years in a 3:1 ratio without replacement. One case had only a single control match, and one case had only two control matches, yielding a total of 66 controls for 23 cases. There was no statistical difference in the distribution of maximum rates of sodium correction in this matched cohort (fisher's exact p = 0.75).			

Discussion

This focused study found: 1) ODS is an uncommon entity in the setting of severe hyponatremia (0.14% incidence in this cohort), consistent with estimates from recent studies[7,13,14]; 2) profound hyponatremia (≤ 105 meq/L) is a dominant independent risk factor for ODS; and 3) marginal differences in the 24-hour rate of sodium correction (e.g. < 8 meq/L vs 8–12 meq/L) in clinical practice have a minor, if not insignificant, association with ODS relative to major ODS risk factors. While a recent publication[15] using similar methodology reported an significant adjusted association between ODS and faster (> 8 mmol/L at 24 hours) sodium correction, that analysis was significantly limited methodologically both by the inclusion of "possible" ODS without radiographic findings and whose symptoms quickly normalized

(accounting for > 60% of cases), and by the inclusion of controls who expired during hospitalization, raising the possibility of confounding by detection bias since slower sodium correction is strongly associated with increased mortality.[5,6,11]

From a clinical perspective, our findings raise concern that an intense focus on controlling sodium correction rates may be distracting clinicians from attending to correctable deficiencies that presage the development of ODS, consistent with observations that ODS occurs both in the absence of hyponatremia or rapid sodium correction.[10,16,17] A potentially treatable commonality between the major ODS risk factors of profound hyponatremia, hypokalemia and alcohol abuse is malnourishment (also recognized as a risk factor) and associated vitamin (i.e. thiamine) and electrolyte deficiencies, as noted in the first published description of central pontine myelinolysis.[18] From a cellular standpoint, the development of ODS appears to be driven by astrocyte apoptosis (and subsequent oligodendrocyte-mediated myelinolysis) due to the inability of astrocytes to compensate for increases in extracellular osmolarity via regulatory volume increase (RVI).[19,20] RVI, in turn, is mediated by active transport of key intracellular electrolytes (potassium, phosphorus) as well as synthesis of organic osmolytes (e.g. taurine, myoinositol), both of which are energy and substrate-dependent processes. As proof of concept, there is experimental evidence that exogenous administration of myoinositol decreases mortality and prevents ODS in rats following rapid sodium correction (30 meq/L/day).[21] Notably, it has been shown that intracellular myoinositol is depleted in advanced liver disease (a risk factor for ODS) but not in the setting of azotemia, corresponding to the relative infrequency of ODS among patients with end-stage renal failure.[22–25] Whether aggressive repletion of intracellular-dominant electrolytes (i.e. potassium and phosphorus) and/or key metabolic co-factors (i.e. thiamine) can similarly mitigate the development of ODS deserves further study, but arguably should be emphasized in treatment pathways for severe hyponatremia as either an indirect means of serum sodium correction (in the case of potassium and phosphorus replacement) or as presumptive treatment of nutritional deficiencies (in the case of thiamine), with little apparent downside.[8]

In summary, the contribution of marginal differences in sodium correction rates on the development of ODS appears to be diminutive and potentially insignificant in comparison to the contribution of major ODS risk factors. Strategies to replenish depleted intracellular protective osmolytes deserve greater emphasis and study.

Data sharing agreement: Data sharing is subject to institutional approval and may be requested by contacting the corresponding author or the Kaiser Permanente Institutional Review Board at kpnc.irb@kp.org.

Declarations

Details Page

1) Confirm that manuscript complies with all instructions to authors: **confirmed**

2) Detailed description of individual author contributions : **study concept and design (DGM, MA, MER), acquisition of the data (MA, DGM), analysis and interpretation of the data (DGM, MA, MER), drafting of the manuscript (DGM), critical revision of the manuscript for important intellectual content (DGM, MA, MER), statistical expertise (DGM, MA, MER), and acquisition of funding (DGM, MER).**

3) Confirm that authorship requirements have been met and the final manuscript was

approved by all authors: **confirmed**

4) Confirm that this manuscript has not been published elsewhere and is not under consideration

by another journal: **confirmed**

5) Confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed: consent, as appropriate. Retrospective studies require a statement regarding IRB

approval: **confirmed**

6) Disclose Conflicts of Interest for all authors: **COI Disclosure: DGM, MA, and MER report no conflicts of interest.**

7) Confirm the use of reporting checklist: **confirmed**

8) List sources of funding for the study: **Financial support: The Permanente Medical Group (TPMG) Rapid Analytics Unit Program.**

9) Artificial intelligence (AI) statment: AI was not used in the writing or development of this manuscript.

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