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Dysnatremia and 6-Month Functional Outcomes in Critically Ill Patients With Aneurysmal Subarachnoid Hemorrhage: A Prospective Cohort Study

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OBJECTIVES: To investigate the association between plasma sodium concentrations and 6-month neurologic outcome in critically ill patients with aneurysmal subarachnoid hemorrhage.

DESIGN: Prospective cohort study.

SETTING: Eleven ICUs in Australia and New Zealand.

PARTICIPANTS: Three-hundred fifty-six aneurysmal subarachnoid hemorrhage patients admitted to ICU between March 2016 and June 2018. The exposure variable was daily measured plasma sodium.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Six-month neurologic outcome as measured by the modified Rankin Scale. A poor outcome was defined as a modified Rankin Scale greater than or equal to 4. The mean age was 57 years (± 12.6 yr), 68% were female, and 32% ($n = 113$) had a poor outcome. In multivariable analysis, including age, illness severity, and process of care measures as covariates, higher mean sodium concentrations (odds ratio, 1.17; 95% CI, 1.05–1.29), and greater overall variability–as measured by the SD (odds ratio, 1.53; 95% CI, 1.17–1.99)–were associated with a greater likelihood of a poor outcome. Multivariable generalized additive modeling demonstrated, specifically, that a high initial sodium concentration, followed by a gradual decline from day 3 onwards, was also associated with a poor outcome. Finally, greater variability in sodium concentrations was associated with a longer ICU and hospital length of stay: mean ICU length of stay ratio (1.13; 95% CI, 1.07–1.20) and mean hospital length of stay ratio (1.08; 95% CI, 1.01–1.15).

CONCLUSIONS: In critically ill aneurysmal subarachnoid hemorrhage patients, higher mean sodium concentrations and greater variability were associated with worse neurologic outcomes at 6 months, despite adjustment for known confounders. Interventional studies would be required to demonstrate a causal relationship.

KEY WORDS: aneurysmal subarachnoid hemorrhage; critical care; hypernatremia; hyponatremia

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) in Australia is estimated at 10 per 100,000 person-years (1). Those affected are relatively young, with a mean age of 55 years, and survivors are likely to have a substantial burden of functional impairment (2, 3).

The commonest electrolyte disturbance in aSAH is dysnatremia, which can manifest as either an elevated or reduced plasma sodium concentration, although hyponatremia is more common (4–6). Hyponatremia may arise from a syndrome of cerebral salt wasting or inappropriate antidiuresis (7, 8). Distinguishing between these two entities is often difficult, and, in practice, management usually consists of avoidance of volume depletion and treatment

with hypertonic solutions (9). Hypernatremia may occur as a result of diabetes insipidus secondary to cerebral injury (10) or secondary to treatment with hypertonic solutions. Intracerebral fluid shifts due to these abnormalities have the potential to lead to poor outcomes (11, 12); however, studies examining the relationship between dysnatremia and outcome have reported conflicting results (4). Therefore, there is uncertainty in how best to manage changes in plasma sodium concentrations in patients with aSAH (13).

We studied a large cohort of critically ill aSAH patients and performed a detailed assessment examining the variability, duration, and trends in plasma sodium concentration and their association with 6-month neurologic outcomes. We hypothesized that both hypernatremia and hyponatremia, as well as the pattern of sodium change, would be associated with differential neurologic outcomes.

METHODS

The Prospective Observational Multicentre Study of Aneurysmal Subarachnoid Haemorrhage in Australia and New Zealand-SAH study was a prospective multicenter observational study of aSAH patients admitted to ICUs in Australia and New Zealand (3). All patients admitted to a participating center, during their initial hospital admission post aSAH, were screened for eligibility. Inclusion/exclusion criteria are provided in **Table S1** (http://links.lww.com/CCX/A653). Ethics approval to undertake the study was obtained at each participating site (Queensland, South Australia, and New South Wales [HREC/16/QRBW/204]; Victoria [HREC/15/Alfred/8]; Western Australia [HREC/16/SCGG/74]; and New Zealand [16/NTB/172]).

Demographics, illness severity (as measured by the Acute Physiology and Chronic Health Evaluation [APACHE] III score), comorbidities, ICU and neurosurgical management, and clinical outcomes were collected prospectively. The severity of the SAH was classified using the World Federation of Neurological Surgeons (WFNS) clinical grading system (14) and Fisher scale (based on the clot burden identified on CT head) (15), as determined by the principal investigator at each site. A high WFNS severity was defined as a WFNS grade of 3 or more. Delayed cerebral ischemia (DCI) was defined as any neurologic deterioration (e.g., hemiparesis, aphasia, altered consciousness) presumed related to ischemia that persisted for more than 1 hour and could not be explained by other physiologic abnormalities noted on standard radiographic, electrophysiologic, or laboratory findings (16).

Daily data collection included fluid balance, the nature and volume of any hypertonic fluids administered, and the use of fludrocortisone and sodium tablets as management strategies for hyponatremia.

Neurologic outcome at 6 months postevent was determined by telephone assessment (by trained staff from either local sites or centrally) using the modified Rankin Scale (mRS) (17).

Measurement of Plasma Sodium

All plasma sodium concentration measurements performed as part of routine clinical care were recorded up to a maximum of 10 per day for each day of the patient's ICU stay. Plasma sodium concentrations obtained from both arterial blood gas analysis and venous blood sample analysis were included. All aspects of the ICU management of the patient, including frequency of blood sampling, were performed at the treating clinician's discretion. Samples were analyzed at each site using local pathology protocols.

Sodium Metrics

Plasma sodium exposure was measured via multiple sodium concentration measurements over the duration of the stay in ICU equating to multiple measures over multiple days. Mean sodium concentration over the stay in ICU was used to quantify sodium exposure and variability in sodium concentrations was evaluated based on the measured SD.

Outcomes

The primary outcome was neurologic outcome at 6 months posthospital discharge, as measured by the mRS. The secondary outcomes were ICU and hospital length of stay (LOS) and incidence of DCI.

Statistical Analysis

All analyses were performed according to a prespecified statistical analysis plan, with continuous data reported as the mean (SD) or median (interquartile range [IQR]), as appropriate, and categorical data as counts

(%). We dichotomized the mRS such that patients with an mRS greater than or equal to 4 were considered to have a poor outcome and patient with mRS less than 4 had a favorable outcome. A death in hospital or within 6 months post discharge was assigned an mRS of 6.

We used multivariable logistic regression to model binary outcomes (poor/favorable outcome as measured by mRS and incidence of DCI) and multivariable negative binomial regression to model count outcomes (hospital and ICU LOS). For the latter models, we report results as mean LOS ratio (MLR). All fitted models were hierarchical with hospital site as a random effect. Regression models examined the association with mean sodium concentration while in ICU and the variability of this concentration and outcome adjusted by predefined covariates including sex, age, WFNS severity, APACHE III score, hours from admission to neurovascular intervention, method of aneurysm obliteration and sodium treatment methods including sodium tablets, fludrocortisone, and sodium fluids (3).

In constructing the regression model of the association of sodium measures with a DCI, only sodium concentrations up until the DCI event were used.

We modeled the longitudinal change in sodium concentration over time using generalized additive models (GAMs) that allow for the functional forms of the models to be nonlinear (18, 19). A GAM takes the strength of generalized linear regression and incorporates additional flexibility informed by the changes in sodium per person over time. Sodium was considered a continuous normally distributed variable over time. GAM models over time allow every sodium reading to contribute to the model at the time (hr) of the reading. We divided the data into two groups based on mRS outcome and constructed two independent GAM models using penalized regression splines and a thin plate smoother with each patient modeled as a random effect and with a fixed-effect covariates set including sex, age, hospital, WFNS severity, APACHE III score, time to intervention, method of securement, and sodium treatment methods.

To account for missing mRS scores, we performed sensitivity analyses in which all missing scores were imputed as mRS greater than or equal to 4 and again as mRS less than 4. Further sensitivity analyses were conducted to assess the impact of deaths within 48 hours on the primary model and the use of other forms of sodium measurements including maximum

and minimum sodium values over the time in ICU, and the proportion of time above or below a prespecified range (upper and lower bounds of 150 and 135 mmol/L, respectively). Further details of methods relating to the sensitivity analyses are presented in the **Supplementary Material** (http://links.lww.com/CCX/A653).

We performed the analyses using R Version 3.6.3 (Vienna, Austria. https://www.R-project.org/) with regressions performed using functions from the lme4 (20) package and GAM analysis performed using mgcv (18).

RESULTS

In 11 neurosurgical referral centers in Australia and New Zealand, between March 2016 and June 2018 (inclusive), we enrolled 359 acute aSAH patients requiring ICU admission. Two patients withdrew consent, and in one patient, sodium measurements were missing, leaving 356 individuals from whom data were available. In 33 patients, there was no recorded mRS and death could not be confirmed (**Fig. S1**, http://links.lww.com/CCX/A653).

The baseline characteristics overall and by neurologic outcome at 6 months are presented in **Table 1**. The mean age of the patients was 57 years (± 12.6 yr) and 68% were female. The proportion of patients presenting with a severe (defined as a WFNS ≥ 3) aSAH was 42%, and 40% of the cohort suffered at least one episode of DCI. The median time of onset of DCI was in the third day after admission to hospital (IQR, 1–6). The proportion of patients with a poor neurologic outcome (defined as mRS ≥ 4 at 6 mo post discharge) was 32%. Over 60% of the patients presenting with a WFNS grade V aSAH were noted to have a poor outcome at 6 months, compared with just under 10% in those patients with a grade I WFNS bleed.

The total number of sodium measurements per person over their time in ICU was 34.0 (SD, 52.6); these were similar regardless of the neurologic outcome (mean 32.9, SD 29.7 vs mean 33.7, SD 22.8 for the mRS ≥ 4 and mRS < 4 groups, respectively, 95% CI of change: –5.5 to 7.1).

Relationship Between Plasma Sodium Concentrations and Outcomes

Multivariable logistic regression analysis was performed based on the two outcome groups (**Table 2**).

TABLE 1.
Baseline Characteristics Overall and by Functional Outcome at 6 Months

Characteristic	mRS ≥ 4, n = 113	mRS < 4, n = 210	Total, n = 356[a]
Age, yr, mean ± SD	60.2 ± 13.1	55.6 ± 12.1	57.0 ± 12.6
Female sex	64.6	68.1	67.7
ICU country			
Australia	58.4	78.4	71.6
New Zealand	41.6	21.4	28.4
World Federation of Neurological Surgeons Grade			
Grade 1	13.3	47.6	34.3
Grade 2	19.5	21.9	23
Grade 3	4.4	5.7	5.1
Grade 4	22.1	12.4	15.2
Grade 5	40.7	12.4	22.5
Acute Physiology and Chronic Health Evaluation III, mean ± SD	65.2 ± 25.1	41.3 ± 19.3	49.1 ± 24.1
Method of securement			
Endovascular coiling/stent	48.7	76.7	66.9
Surgical clipping	23.9	23.3	24.4
None	27.4	0	8.7
Interval from admission to neurovascular intervention (hr)	17.7 (21.9)	13.9 (9.8)	14.9 (14.25)
Length of ICU stay (d)	9.0 (9)	6.0 (12)	9.0 (10)
Length of hospital stay (d)	10 (23)	22 (13)	20 (16)
Proportion of patients diagnosed with delayed cerebral ischemia	42.5	41.0	40.4

mRS = modified Rankin Scale.

[a]Thirty-three mRS values were missing. See **Supplementary Appendix** (http://links.lww.com/CCX/A653) for sensitivity analyses. Durations in hours and days are given as median (interquartile range). All other numbers given are percentages.

An increase in mean sodium concentration throughout the time spent in ICU (odds ratio [OR], 1.17; 95% CI, 1.05–1.29) and greater variability (expressed as SDs) in sodium concentrations (OR, 1.53; 95% CI, 1.17–1.99) were associated with poor outcome. Poor outcomes were also associated with an increase in age (OR, 1.06; 95% CI, 1.03–1.09), an increase in APACHE III score (1.02; 95% CI, 1.00–1.04), and a prolonged interval between admission and neurovascular intervention in hours (OR, 1.01; 95% CI, 1.00–1.02).

Relationship Between Plasma Sodium Concentrations and Secondary Outcomes

Associations between the mean sodium concentration and SD, and the incidence of DCI were identified by multivariable logistic regression (**Table S2**, http://links.lww.com/CCX/A653). Mean sodium concentrations and variability of these concentrations were not associated with the incidence of DCI (mean sodium: OR, 0.95; 95% CI, 0.86–1.04 and SD of sodium: OR, 1.06; 95% CI, 0.82–1.37).

LOS in ICU and LOS in hospital were modeled as multivariable negative binomials adjusted for the same covariate as the primary outcome (**Table S3**, http://links.lww.com/CCX/A653). Increased variability in sodium concentration was associated with longer stays in both ICU and hospital with MLR (1.13; 95% CI, 1.07–1.20 and 1.08; 95% CI, 1.01–1.15, respectively.) There was no statistically significant association between mean sodium concentration and either ICU or hospital LOS. Admission with a high WFNS value, a longer time from admission to neurovascular intervention and the need for surgical clipping all had a positive association with an extended LOS in both ICU and the hospital in general.

TABLE 2.
Multivariable Model

Characteristic	OR (95% CIs)	p
Mean sodium	1.17 (1.05–1.29)	0.003
SD of sodium	1.53 (1.17–1.99)	0.002
Male	1.41 (0.72–2.79)	0.321
Age	1.06 (1.03–1.09)	> 0.001
High World Federation of Neurosurgeons Score severity	1.79 (0.88–3.68)	0.120
Acute Physiology and Chronic Health Evaluation III score	1.02 (1.00–1.04)	0.007
Hours from admission to neurovascular intervention	1.01 (1.00–1.02)	0.036
Surgical clipping	1.78 (0.86–3.66)	0.120
Treated with sodium tablets (600 mg sodium per tablet)	0.47 (0.16–1.40)	0.174
Treated with fludrocortisone	1.93 (0.55–6.76)	0.305
Treated with hypertonic sodium fluids	0.93 (0.39–2.24)	0.873

OR = odds ratio.
High severity was defined as a World Federation of Neurosurgeons Score ≥ 3.

TABLE 3.
Sodium Treatment While in ICU

Characteristic	mRS < 4 (n = 210)	mRS ≥ 4 (n = 113)	Total (n = 323)
Any sodium treatment			
Percent untreated (%)	47.6	28.3	40.9
Sodium tablets (600 mg sodium per tablet)			
Percent treated (%)	30.5	10.6	23.5
Mean number of tablets per day (SD)	7.2 (3.3)	7.2 (2.2)	7.2 (3.1)
Fludrocortisone			
Percent treated (%)	10.5	6.2	9.0
Mean fludrocortisone doses per day in μg (SD)	238.3 (136.8)	241.0 (145.6)	229.6 (131.6)
Hypertonic saline			
Percent treated with either 3% or 20% saline (%)	34.8	26.5	31.9
Percent treated with 3% saline (%)	22.4	11.5	18.6
Mean volume of 3% saline administered per day in mL (SD)	496.0 (351.1)	505.6 (414.1)	511.4 (371.1)
Percent treated with 20% saline (%)	8.1	9.7	8.7
Mean volume of 20% saline administered per day in mL (SD)	61.3 (47.1)	60.6 (43.5)	46.3 (48.0)
Other forms of sodium treatment			
Percent treated (%)	7.1	8.0	7.4

mRS = modified Rankin Scale.

Use of Sodium Treatments While in ICU

Just under 60% of patients received some form of sodium treatment while in ICU, with a greater proportion of patients with a favorable outcome receiving treatment compared with a poor outcome (47.6% and 28.3%, respectively) (**Table 3**). Nearly 25% of people were treated with sodium tablets (containing 600 mg sodium per tablet), and if treated, a mean of 7.2 tablets (SD 3.1) were received each day. The mean fludrocortisone dose for

the 9% of patients was nearly 230 µg/d (sᴅ 131.6 µg/d). Between 25% and 35% of patients were treated with some form of hypertonic saline, with 3% of saline being more commonly administered than 20% saline.

Sodium Changes Over Time Using Generalized Additive Models

The change in plasma sodium for the two outcome groups was measured from admission to ICU discharge. The shapes of the functional forms of sodium concentration over time are shown in **Figure 1**. Patients with a favorable 6-month mRS outcome (Fig. 1*A*) displayed a comparatively stable sodium concentration over time, between 137 and 143 mmol/L. Patients with a poor 6-month mRS outcome (Fig. 1*B*) had a marked downward trajectory in sodium from day 3 (144 mmol/L) to day 16 in ICU (136 mmol/L) and a greater amount of variability within the functional form. A plot of residual against predicted values for the change in sodium concentration over time for the two outcome groups is presented in **Figure S2** (http://links.lww.com/CCX/A653).

Sensitivity Analyses

Sensitivity analyses were performed to assess the impact of missing outcomes (**Table S4**, http://links.lww.com/CCX/A653), as well as the sodium concentration summarization method (**Table S5**, http://links.lww.com/CCX/A653). Further sensitivity analysis was performed by censoring the 29 patients who died within 48 hours of arriving in ICU (**Table S6**, http://links.lww.com/CCX/A653). Results indicate no significant differences in the models.

DISCUSSION

A higher mean value and greater variability in plasma sodium concentrations while in ICU were associated with a greater likelihood of a poor neurologic outcome at 6 months in critically ill aSAH patients. Furthermore, a high initial sodium concentration, followed by a gradual decline from day 3 onwards, was the specific pattern observed in those with a poor outcome. Finally, mean and variability of sodium concentrations while in ICU were not significantly associated with the risk of DCI, but increased sodium variability was associated with a longer ICU and hospital LOS.

The relationship between plasma sodium concentrations and neurologic outcomes in aSAH remains a matter of debate. Previous studies have reported that high sodium concentrations (5, 21) and greater variability (22) are associated with worse neurologic outcomes and mortality in aSAH, and our findings replicate this.

Hypernatremia may reflect severe brain injury resulting in diabetes insipidus or may be a marker of treatment with hyperosmolar therapy for cerebral edema, both of which are plausibly associated with worse 6-month outcomes (23). Equally, increased variability may reflect the consequence of attempts to correct hypernatremia with hypotonic fluids or attempts to correct hyponatremia with hypertonic solutions.

The predictive value of hyponatremia in aSAH is less clear. Several studies have reported that hyponatremia is associated with a greater risk of developing
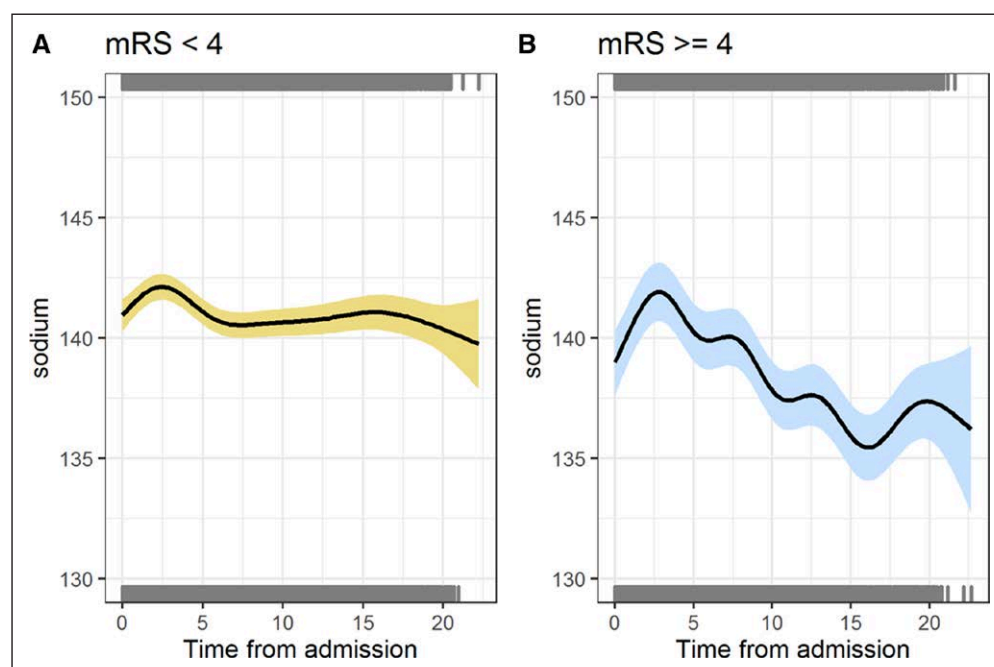
FIGURE 1. Generalized additive models—predicted sodium values over time by modified Rankin Scale (mRS) category (color bands are 95% CIs). Time from admission is in days. Sodium values are in mmol/L.

cerebrovascular spasm or cerebral infarction (24–26). However, other studies have found no relationship between hyponatremia and functional outcome or mortality (5, 27). There are several potential explanations for this discrepancy. This includes: 1) differences in how hyponatremia is defined (which can be categorized as either present or absent or by varying threshold values and varying numbers of samples), 2) reporting of analyses and models that do not account for duration or severity (e.g., temporal changes over the course of an admission), and 3) use of variable outcome measures, with only a few studies reporting on long-term neurologic status.

Our nonlinear analyses showed marked differences in the patterns of sodium concentration over the course of the ICU stay between patients with favorable and poor outcomes. Those who did poorly manifested an initial peak of sodium concentrations followed by a steady decline. This may represent an initial period of cerebral damage resulting in a later syndrome of inappropriate antidiuretic hormone secretion. In contrast, patients with a favorable outcome exhibited a much more stable sodium trajectory. To our knowledge, this is the first description of this phenomenon in aSAH patients.

Our findings imply that hypernatremia and greater sodium variability, as well as the trajectory of these values over time in critically ill aSAH patients, are associated with poor neurologic outcomes at 6 months. Given that rapid changes in sodium concentrations are known to be associated with osmotic shock-induced neuronal damage, (28) our findings provide the additional epidemiological rationale for future interventional studies aimed at minimizing variability, and maintaining a steady trajectory in plasma sodium concentrations, in this patient group.

Our study has several strengths. We have collected data prospectively from multiple centers across Australia and New Zealand and obtained a large number of data points for analysis. We have used several analytical techniques considering variability, duration and severity and temporal fluctuations in sodium concentrations, with a robust patient-centered primary outcome of 6-month neurologic status.

Limiting our conclusions, as with any observational work, is the fact we cannot infer any causative relationship. Our primary outcome measure may not detect small, but clinically important, outcome differences. Our analysis is hypothesis-generating, and therefore,

we did not formally correct for multiple comparisons. Reported secondary outcomes should therefore be interpreted cautiously. Additionally, our strategy used sodium measurements taken for clinical purposes that may have led to a sampling bias, although the number of measurements collected was similar in the two outcome groups. The use of different sampling methods may also have influenced our results. Point of care testing using direct ion-selective electrodes may be more accurate than indirect techniques commonly used in hospital laboratories, especially in hypoproteinemia, commonly seen in critically ill patients (29). Discrepancies between these techniques may have potentially contributed to the variation in sodium measurements we observed.

CONCLUSIONS

In critically ill patients with aSAH, a pattern of initial high sodium concentrations followed by gradual decline was associated with a worse neurologic outcome at 6 months. A higher mean sodium concentration, and greater variability in ICU, were also associated with worse outcomes. These findings provide the epidemiological rationale for future interventional studies aimed at minimizing plasma sodium variability in this patient group.

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