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Association of Hyponatremia on Mortality in Cryptococcal Meningitis: A Prospective Cohort

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Background. Sodium abnormalities are frequent in central nervous system infections and may be caused by cerebral salt wasting, syndrome of inappropriate antidiuretic hormone secretion, or medication adverse events. In cryptococcal meningitis (CM), the prevalence of baseline hyponatremia and whether hyponatremia adversely impacts survival is unknown.

Methods. We conducted a secondary analysis of data from 2 randomized trials of human immunodeficiency virus–infected adult Ugandans with CM. We grouped serum sodium into 3 categories: <125, 125–129, and 130–145 mmol/L. We assessed whether baseline sodium abnormalities were associated with clinical characteristics and survival.

Results. Of 816 participants with CM, 741 (91%) had a baseline sodium measurement available: 121 (16%) had grade 3–4 hyponatremia (<125 mmol/L), 194 (26%) had grade 2 hyponatremia (125–129 mmol/L), and 426 (57%) had a baseline sodium of 130–145 mmol/L. Hyponatremia (<125 mmol/L) was associated with higher initial cerebrospinal fluid (CSF) quantitative culture burden ($P < .001$), higher initial CSF opening pressure ($P < .01$), lower baseline Glasgow Coma Scale score ($P < .01$), and a higher percentage of baseline seizures ($P = .03$). Serum sodium <125 mmol/L was associated with increased 2-week mortality in unadjusted and adjusted survival analyses (adjusted hazard ratio, 1.87 [95% confidence interval, 1.26–2.79]; $P < .01$) compared to those with sodium 130–145 mmol/L.

Conclusions. Hyponatremia is common in CM and is associated with excess mortality. A standardized management approach to correctly diagnose and correct hyponatremia in CM needs to be developed and tested.

Keywords. cryptococcal meningitis; hyponatremia; mortality; prognostic marker; sodium.

Hyponatremia is the most frequent electrolyte abnormality in central nervous system (CNS) disease, resulting from failure of neuroendocrine regulatory mechanisms to maintain salt and water balance [1]. Coupled with CNS disease, hyponatremia may exacerbate cerebral edema and increase intracranial pressure due to hypo-osmolality [2]. There are 2 main mechanisms of hyponatremia in CNS disease; the first is cerebral salt wasting caused by excess brain natriuretic peptide leading to renal salt wasting and a volume contracted state; the second is the syndrome of inappropriate antidiuretic hormone (ADH) secretion

(SIADH), a volume-expanded state from ADH-mediated water retention [3]. Differentiating cerebral salt wasting from SIADH is complex but important for management as treatment for SIADH with fluid restriction would be detrimental in the volume contracted state of cerebral salt wasting. Ultimately, the ability to determine the volume status (low vs high effective arterial blood volume) is pivotal in differentiating between cerebral salt wasting and SIADH.

Hyponatremia in the context of CNS infections has been well documented in tuberculous meningitis (TBM). Approximately 40%–50% of TBM patients present with hyponatremia, which is most commonly attributed to cerebral salt wasting [3, 4]. Sodium levels <125 mmol/L, among adults with TBM, are associated with up to a 3-fold increase in mortality compared to normal sodium levels [5]. Hyponatremia in CNS cryptococcosis, however, has not been well described. Published literature on the topic of hyponatremia in cryptococcal meningitis (CM) is limited to a few case reports in which cases of both cerebral salt wasting and SIADH are described [6–9]. In the published literature, sodium levels and the general condition of patients with clinical and laboratory findings consistent with

cerebral salt wasting improved with administration of isotonic saline and fludrocortisone, whereas those with SIADH improved with treatment of CM.

Severe hyponatremia, irrespective of the cause, may cause altered mental status, which in itself is an independent predictor of cryptococcal mortality [10]. However, it is unclear whether hyponatremia is independently associated with adverse clinical outcomes in CM. In this prospective study of adults with human immunodeficiency virus (HIV)–associated CM in Uganda, we assessed whether baseline sodium abnormalities are associated with excess mortality.

METHODS

We conducted a prospective cohort study of adult Ugandans with HIV-associated CM from 2015 to 2020 as a secondary analysis of 2 randomized trials, the Adjunctive Sertraline for HIV-Associated Cryptococcal Meningitis trial (ASTRO-CM) and the AMBIsome Therapy Induction Optimisation trial (AMBITION) [11, 12]. All participants with suspected meningitis were screened for enrollment into ASTRO-CM and those found to have a first episode of CM were enrolled into the randomized trial. Participants found to have CM relapse were consented to receive open-label, compassionate use of sertraline. In the ASTRO-CM trial, participants were randomly assigned (1:1) to receive standard therapy with 7–14 days of intravenous amphotericin B and oral fluconazole with either adjunctive sertraline or placebo. Participants enrolled in the AMBITION trial were randomly assigned (1:1) to receive a single high dose of liposomal amphotericin B (AmBisome, Gilead Sciences) in combination with 14 days of fluconazole and flucytosine or 7 days of standard amphotericin B deoxycholate in combination with 7 days of flucytosine followed by 7 days of high-dose fluconazole. For both trials, participants were enrolled from 2 referral hospitals in Kampala and Mbarara with follow-up for at least 10 weeks. Both trials are described in detail elsewhere [12, 13].

A diagnosis of CM was made based on a positive cryptococcal antigen test (CrAg lateral flow assay, IMMY) in both the serum and cerebrospinal fluid (CSF). All participants found to have an elevated CSF protein and clinical features suggestive of TBM had a CSF Xpert MTB/RIF Ultra assay performed at baseline. Serum sodium was measured for all enrolled participants at baseline and at day 7 and day 14 from initiation of antifungal therapy. All participants routinely received at least 1 L of intravenous normal saline (0.9% sodium chloride) before and after each infusion of amphotericin, which itself was administered in 1 L of 5% dextrose.

Patient Consent Statement

The design of both clinical trials was approved by local ethical committees and conformed to Ugandan clinical trial standards.

Approval for the ASTRO-CM trial was obtained from the Uganda National Council for Science and Technology, the Mulago Institutional Review Board (IRB) in Uganda, and the IRB at the University of Minnesota. Approval for the AMBITION trial was obtained from the London School of Hygiene and Tropical Medicine Research Ethics Committee and the Mulago IRB in Uganda. All participants provided written informed consent at time of cryptococcal diagnosis for study participation.

We assessed whether baseline sodium abnormalities were associated with excess mortality. We categorized serum sodium levels as normal or grade 1 (130–145 mmol/L), grade 2 (125–129 mmol/L), and grade 3–4 (<125 mmol/L) hyponatremia per the National Institute of Allergy and Infectious Diseases Division of AIDS toxicity table (version 2.1, July 2017) [14]. Four sodium values >150 mmol/L and 4 sodium values between 146 and 150 mmol/L were excluded from the comparator group as they were considered to be above the normal serum sodium range. The primary outcome was time from the baseline sodium measurement to death in the first 2 weeks. We additionally assessed 30-day mortality.

We summarized baseline demographic variables and clinical characteristics by serum sodium group using percentages and medians with interquartile range (IQR). We compared medians with the Kruskal-Wallis test and proportions with the χ^2 test. We examined the association between baseline sodium and survival using Cox proportional hazards models and Kaplan-Meier curves. All models were adjusted for the following variables defined a priori: Glasgow Coma Scale (GCS) score <15 vs 15, baseline CSF cryptococcal quantitative culture, and study. A 2-sided type I error of .05 was used. We performed all analyses with SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

From March 2015 to May 2017, a total of 524 participants were enrolled in the ASTRO-CM trial, and from October 2018 to February 2020, a total of 308 were enrolled in the Uganda sites of the AMBITION trial. No trial participants had microbiologically confirmed cryptococcal and TBM coinfection. Among 816 trial participants, 749 (92%) had serum sodium measured at baseline, of which 99% (741/749) had a serum sodium ≤145 mmol/L and were included in this analysis. More than half (52.2% [n = 426]) of participants had normal or grade 1 baseline sodium 130–145 mmol/L, 23.8% (n = 194) had grade 2 hyponatremia (125–129 mmol/L), and 14.8% (n = 121) had grade 3–4 hyponatremia (<125 mmol/L). Eight participants (0.01% [n = 8]) had a baseline serum sodium ≥145 mmol/L, were classified with hypernatremia, and were excluded from this analysis. Median sodium was 134 mmol/L (IQR, 132–137) among those with grade 1 baseline sodium, 128 mmol/L

(IQR, 126–128) among those with grade 2, and 122 mmol/L (IQR, 119–123) among those with grades 3–4. Overall, serum sodium levels improved over time within all 3 sodium categories (Supplementary Tables 1–4).

Baseline demographics and clinical characteristics are summarized by the severity of hyponatremia in Table 1. Hyponatremia was found to be associated with altered mental status (GCS score <15) and self-reported seizures at baseline. Half (52.5%) of the participants with sodium <125 mmol/L presented with GCS score <15 as compared to 45.1% of participants with sodium 125–129 mmol/L and 35.5% with sodium 130–145 mmol/L ($P < .01$). Participants with severe hyponatremia were also more likely to present with a history of self-reported seizures at baseline (24.2% with sodium <125 mmol/L vs 13.5% with sodium 125–129 mmol/L vs 15.2% with sodium 130–145; $P = .03$). Hyponatremia was also associated with increased CSF opening pressures ($P < .01$) and a higher CSF fungal burden. CSF cryptococcal quantitative culture was significantly greater in persons with severe hyponatremia at baseline (median, 4.8 [IQR, 4.2–5.9] $\log_{10}$ colony-forming units [CFU]/mL for sodium <125 mmol/L; median, 4.7 [IQR, 2.8–5.4] $\log_{10}$ CFU/mL for sodium 125–129 mmol/L; and median, 4.3 [IQR, 2.4–5.5] $\log_{10}$ CFU/mL for sodium 130–145 mmol/L; $P < .001$).

Severe hyponatremia (sodium <125 mmol/L) was associated with mortality in both unadjusted and adjusted survival analyses. The proportion of deaths occurring by 2 weeks is higher in severe hyponatremia (<125 mmol/L) at 39.7%, compared to 24.2% in moderate hyponatremia (125–129 mmol/L) and 16.9% with sodium 130–145 mmol/L (χ^2 test, $P < .001$; Table 2).

When compared to participants with baseline sodium 130–145 mmol/L, a baseline sodium <125 mmol/L was associated with nearly 2-fold higher 2-week mortality (adjusted hazard ratio [aHR], 1.87 [95% confidence interval {CI}, 1.26–2.79]; $P < .01$) and 30-day mortality (aHR, 1.88 [95% CI, 1.33–2.66]; $P < .001$) (Table 2). Overall, cumulative probability of 2-week survival was lowest in the severe hyponatremia group (<125 mmol/L) as illustrated in Figure 1.

DISCUSSION

Among Ugandan adults with CM enrolled in 2 clinical trials, we observed that severe baseline hyponatremia (<125 mmol/L) is common and associated with nearly 2-fold higher in-hospital mortality. This risk is consistent when assessing 2-week and 30-day mortality. This is not surprising as severe hyponatremia is a well-established poor prognostic indicator in TBM, bacterial meningitis, and among critically ill patients in general [5, 15, 16]. Our study is the first to confirm that baseline severe hyponatremia is also a poor prognostic indicator in CM and may act as a surrogate marker of severe CM.

Our study population was comprised of individuals with CM in the context of advanced HIV disease; therefore, the etiology of hyponatremia is likely multifactorial including non-CNS complications of advanced HIV disease such as poor intake, gastrointestinal losses, drugs, endocrine disorders, liver, kidney, and heart failure. Although non-CNS causes of hyponatremia is possible, we hypothesize that in CM, CNS cryptococcosis directly leads to the development of hyponatremia. While we were unable to differentiate between cerebral salt wasting and

Table 1. Baseline Characteristics

Characteristic	Na+ <125 mmol/L		Na+ 125–129 mmol/L		Na+ 130–145 mmol/L		
	No.	Median (IQR) or No. (%)	No.	Median (IQR) or No. (%)	No.	Median (IQR) or No. (%)	P Value[a]
Age, y	121	36 (30–43)	194	35 (30–42)	426	35 (29–40)	**.04**
Male sex, No. (%)	121	85 (70.2)	194	118 (60.8)	426	240 (56.3)	**.02**
Receiving HIV therapy, No. (%)	121	68 (56.2)	194	85 (43.8)	426	217 (50.9)	.08
GCS score <15, No. (%)	120	63 (52.5)	193	87 (45.1)	422	150 (35.5)	**<.01**
Seizure, No. (%)	120	29 (24.2)	193	26 (13.5)	422	64 (15.2)	**.03**
Prior CM, No. (%)	120	10 (8.3)	194	13 (6.7)	420	21 (5.0)	.35
CD4 count, cells/μL	115	21 (6–43)	184	17 (7–47)	402	20 (8–53)	.45
Hemoglobin, g/dL	120	12 (10–13)	186	11 (10–13)	421	11 (10–13)	.23
Creatinine, mg/dL	121	0.6 (0.6–0.8)	193	0.8 (0.6–0.9)	424	0.7 (0.6–0.9)	**<.001**
CSF white cells/μL	119	<5 (<5–40)	182	<5 (<5–45)	408	<5 (<5–55)	.41
CSF white cells <5/μL, No. (%)	119	76 (63.9)	182	111 (61.0)	408	234 (57.4)	.39
CSF protein, mg/dL	100	40 (23–94)	162	50 (25–98)	365	74 (37–118)	**<.01**
CSF glucose, mg/dL	57	67 (39–84)	76	47 (33–86)	254	64 (41–85)	.09
Opening pressure, cm water	113	27 (18–38)	173	25 (17–37)	380	23 (15–34)	**<.01**
CSF culture, $\log_{10}$ CFU/mL	120	4.8 (4.2–5.9)	191	4.7 (2.8–5.4)	415	4.3 (2.4–5.5)	**<.001**
CSF removed, mL	118	15 (9–22)	187	14 (8–19)	386	12 (8–18)	**.01**

Abbreviations: CFU, colony-forming units; CM, cryptococcal meningitis; CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; HIV, human immunodeficiency virus; IQR, interquartile range; Na+, Sodium.

[a]P value by Kruskal-Wallis or χ^2 test. Values in bold indicate a P-value less than 0.05.

Table 2. Survival Outcomes by Baseline Serum Sodium Group

Outcome	Na+ <125 mmol/L	P Value	Na+ 125–129 mmol/L	P Value	Na+ 130–145 mmol/L
Deaths within 2 wk					
No. of overall patients	121		194		426
No. (%) with death	48 (39.7)		47 (24.2)		72 (16.9)
Event rate (95% CI)[a]	1.10 (.79–1.41)		0.62 (.44–.79)		0.41 (.31–.50)
HR (95% CI)[b]					
Model 1	2.61 (1.81–3.77)	<.001	1.51 (1.04–2.17)	.03	Ref
Model 2	1.98 (1.34–2.92)	<.001	1.38 (.94–.01)	.10	Ref
Model 3	1.87 (1.26–2.79)	<.01	1.31 (.89–.93)	.17	Ref
Deaths within 30 d					
No. of overall patients	121		194		426
No. (%) with event	61 (50.4)		61 (31.4)		97 (22.8)
Event rate (95% CI)[a]	0.78 (.58–.97)		0.41 (.31–.52)		0.27 (.22–.33)
HR (95% CI)[b]					
Model 1	2.62 (1.90–3.61)	<.001	1.48 (1.07–2.04)	.02	Ref
Model 2	2.07 (1.47–2.90)	<.001	1.35 (.97–1.87)	.08	Ref
Model 3	1.88 (1.33–2.66)	<.001	1.24 (.89–1.74)	.21	Ref

Abbreviations: CI, confidence interval; HR, hazard ratio; Na+, Sodium; Ref, Reference.

[a]Rate per 30 person-days.

[b]Model 1, unadjusted; model 2, adjusted for Glasgow Coma Scale (GCS) score and cerebrospinal fluid quantitative culture; model 3, adjusted for GCS score, culture, and study cohort.
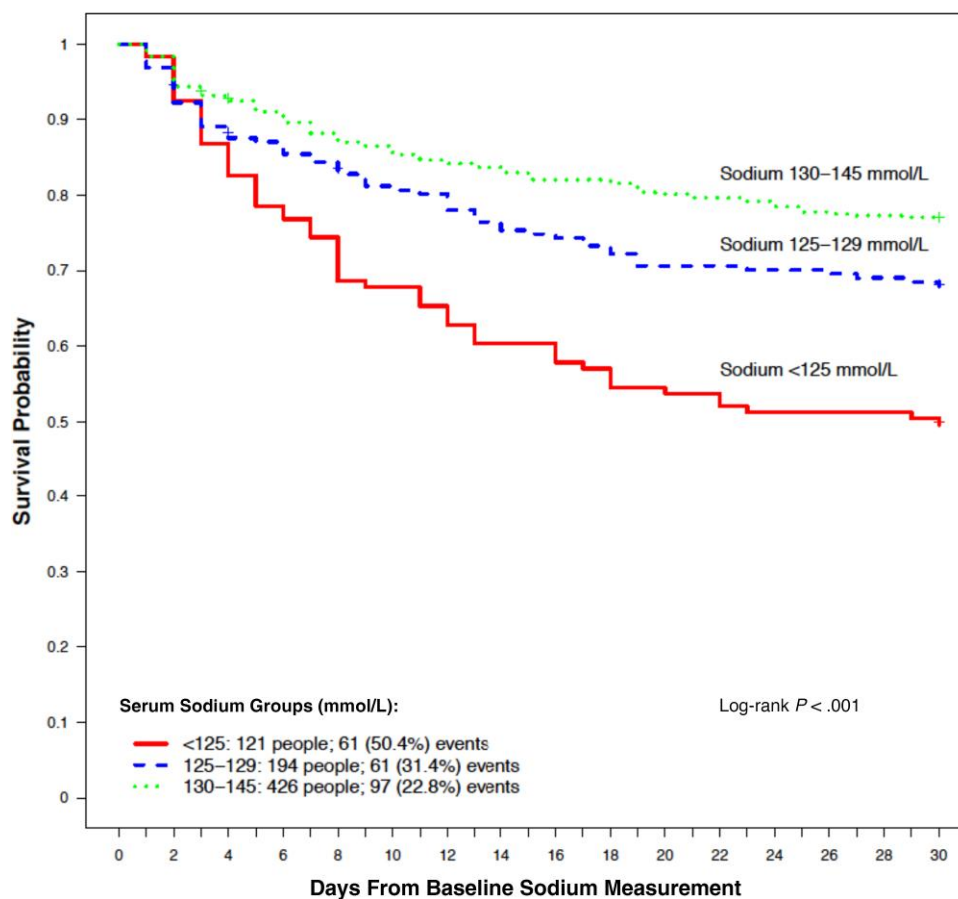

Figure 1. Thirty-day survival by baseline serum sodium category.

SIADH in our studies, we observed that individuals with severe hyponatremia present with more severe CNS disease as characterized by altered mental status, seizures, elevated intracranial pressures, and higher CSF fungal burden. Thus, it is highly likely that baseline hyponatremia, in this cohort, is attributable to CNS cryptococcosis as opposed to non-CNS causes. Further, baseline hyponatremia may be used as a surrogate marker of increased intracranial pressures, especially in settings where manometers are not available to measure opening pressures.

The evaluation of hyponatremia in our studies was limited by the lack of access to testing of urine electrolytes, serum osmolality, and acid-base status, as these are not readily available in settings where the burden of CM is highest. Furthermore, CM guidelines for resource-limited settings focus on the management of electrolyte imbalances of potassium and magnesium with no mention to the evaluation and management of hyponatremia. A rational approach to evaluating the etiology

of hyponatremia in persons presenting with CM would be to initially exclude non-CNS causes of hyponatremia followed by differentiation between SIADH and cerebral salt wasting to determine the optimal treatment. We suggest a pragmatic approach to the evaluation and management of severe hyponatremia among patients with CM presenting with serum sodium <125 mmol/L that can be easily implemented in both low- and high-resource settings (Figure 2).

In CM, symptoms of severe hyponatremia including altered mental status and seizures are common and occurs with moderate frequency. Treatment of CM, including management of raised intracranial pressure, seizures, and initiation of amphotericin-based antifungal therapy, will lead to early improvement of hyponatremia in most cases. Amphotericin therapy requires specific consideration, as (1) preexisting hyponatremia predisposes to declines in glomerular filtration rate, thereby exacerbating electrolyte abnormalities; and
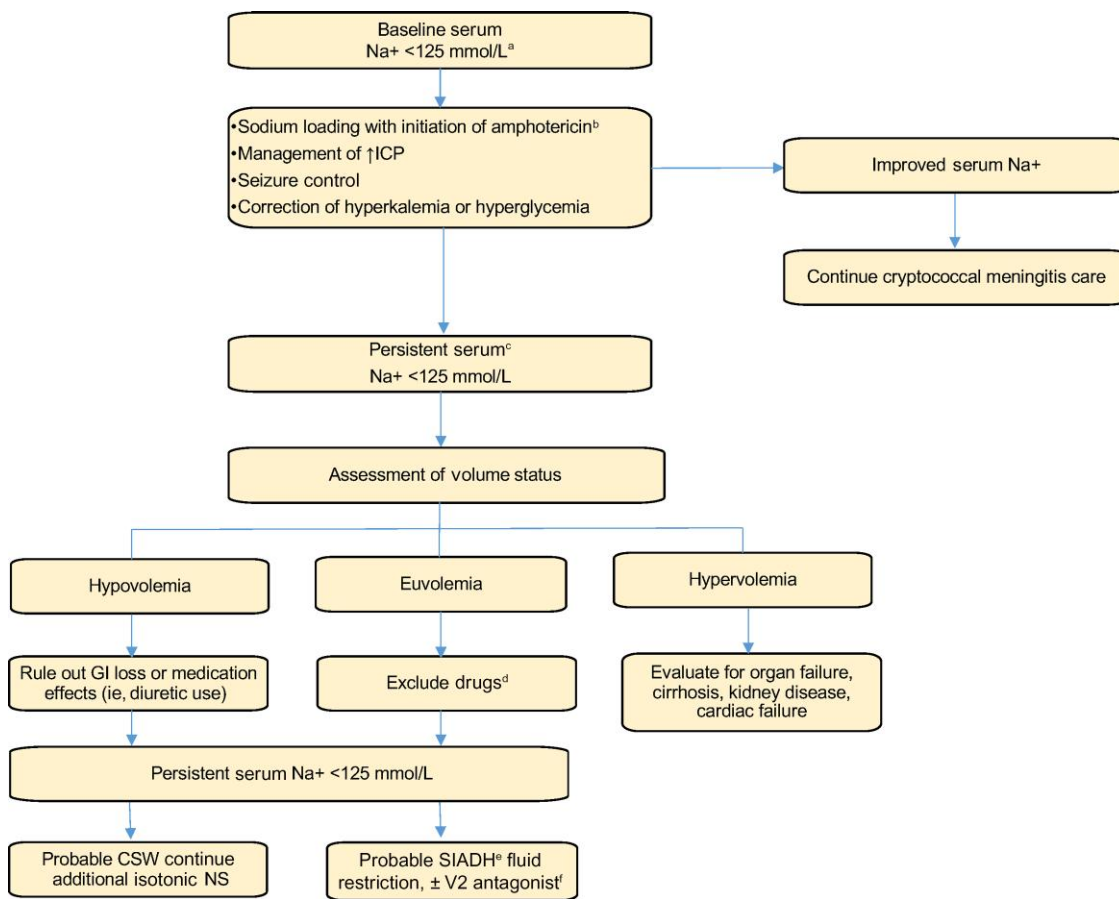
Figure 2. Pragmatic approach to the evaluation and management of severe hyponatremia in adults with human immunodeficiency virus–associated cryptococcal meningitis (CM). [a]Monitoring of serum sodium (Na+) recommended daily until stable. [b]Initiation of amphotericin-based antifungal therapy requires administration of normal saline prior to and after infusion. Correction of serum Na+ levels is less urgent in the first 48 hours as patients with chronic hyponatremia are at risk of osmotic demyelination syndrome. [c]Persistent serum Na+ <125 mmol/L by day 7 of CM care. [d]Excludes drugs known to enhance activity of arginine vasopressin including carbamazepine. [e]Patients with syndrome of inappropriate antidiuretic hormone secretion may respond to continued treatment of CM. [f]Vasopressin receptor antagonist. Abbreviations: CSW, Cerebral salt wasting; GI, Gastrointestinal; ICP, Intracranial pressure; Na+, Sodium; NS, Normal Saline; SIADH, syndrome of inappropriate antidiuretic hormone secretion; V2, vasopressin.

(2) administration of 500–1000 mL of 0.9% sodium chloride (normal saline) prior to and after amphotericin infusion is needed to prevent nephrotoxicity. If hyponatremia persists with initiation of cryptococcal therapy, the assessment of volume status will be crucial in differentiating between either cerebral salt wasting or SIADH and directing the appropriate management.

Mortality among inpatients with HIV-associated CM remains high (approximately 20%) even with the most efficacious antifungals currently available in sub-Saharan Africa. Our group has previously shown that increased CSF lactate and low cerebral tissue oxygenation are associated with excess mortality in CM [17–19]. Taken together, these findings suggest that optimizing neurological supportive care or critical care among patients with CM in resource-limited settings, in addition to providing optimal antifungal therapy, could further improve treatment outcomes.

Our study is not without limitations. We did not have enough data to determine the etiology and pathophysiological mechanism of hyponatremia. Our statistical analysis was unable to include baseline opening pressure as a covariate in the adjusted mortality models as we would have had to exclude a significant number of participants from our analysis due to missing data. While we recognize that this is a significant limitation, given that the association between baseline severe hyponatremia and mortality is preserved even after adjusting for previously known predictors of mortality and increased intracranial pressures including altered mental status and high baseline fungal burden, we feel confident in our results [20]. Of note, all study participants, irrespective of sodium level, routinely received at least 154 mmol/L of sodium given as 1 L of 0.9% intravenous saline before and after amphotericin administration, which may also treat mild to moderate hyponatremia secondary to cerebral salt wasting. In the event that persons with CM present with cerebral salt wasting, receiving normal saline may bias mortality risk toward the null. The reverse would be true for SIADH and other causes of hyponatremia associated with high effective arterial blood volume. This underscores the importance of determining the cause of hyponatremia in future studies.

In summary, hyponatremia is a common presentation and poor prognostic indicator in HIV-associated CM. Our findings also suggest that individuals with low sodium levels present with more severe CNS disease. Further studies investigating the pathophysiological mechanism leading to hyponatremia is warranted as optimal supportive therapy to correct hyponatremia may improve outcomes.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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