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Clinical Study

Risk factors for hyponatremia in aneurysmal subarachnoid hemorrhage

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ABSTRACT

Hyponatremia occurs commonly in patients with aneurysmal subarachnoid hemorrhage (aSAH). Our objective was to determine the time course of, and factors associated with, hyponatremia after aSAH. We performed a retrospective review of 259 patients with ruptured aneurysms at a single institution. Multivariate regression analysis was performed to determine the factors associated with hyponatremia. Increasing age was significantly associated with lower initial sodium ($p = 0.04$) and incidence of delayed hyponatremia ($p = 0.01$) while smoking was associated with longer duration of hyponatremia ($p = 0.02$). Older patients should therefore be monitored closely for hyponatremia and patients who smoke should be treated more aggressively for hyponatremia given the greater frequency and longer duration of hyponatremia in these two groups, respectively.

1. Introduction

Between one third and one half of patients with aneurysmal subarachnoid hemorrhage (aSAH) develop hyponatremia during their hospitalization [1,2]. However, the etiology of delayed hyponatremia continues to be debated, partly due to the unclear time-course of hyponatremia, as well as a lack of more definitive molecular biochemical studies [1]. Mechanistic theories include cerebral salt wasting (CSW), the syndrome of inappropriate anti-diuretic hormone (SIADH), glucocorticoid insufficiency, iatrogenic fluid overload or excessive diuretics [1,3–5]. Approximately 40% of patients develop hyponatremia within the first 3 days of hemorrhage, while about 30% of patients develop hyponatremia 1 week following rupture [3]. No studies currently report on serum sodium levels upon presentation of aSAH and there is a paucity of investigations into risk factors or pathophysiology of hyponatremia in these patients [3]. In this study, we evaluated the prevalence of early and late hyponatremia, and risk factors for its occurrence.

2. Methods

We retrospectively reviewed the records of 259 consecutive patients with aSAH from a single academic institution. Demographics, aneurysm location, presenting clinical examination defined by Hunt-Hess grade (categorized as 1–3 or 4–5), intraventricular hemorrhage, treatment approaches by endovascular coiling or microsurgical clipping, and serum sodium were extracted from the medical records. Patients with aSAH at our institution undergo at least daily serum sodium evaluation while those with significant hyponatremia undergo testing at least four times daily. This study has been approved by our institutional review board.

2.1. Statistical methods

Univariate analysis was performed using linear regression for continuous outcome measures (initial serum sodium and duration of hyponatremia) and logistic regression for the binary outcome measure, hyponatremia defined as serum sodium $\leqslant$134 mEq. Variables which were at or near significance ($p \leqslant 0.2$) in the univariate analyses were included in a multivariate regression model. Statistical significance was set with a threshold of $p < 0.05$. Analysis was completed in R (v3.0) (R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Demographics

Across our 259 patient cohort, the median patient age was 54 and there was a female sex predilection (76%, Table 1). Half of the patients (49%, n = 128) presented with Hunt-Hess grades 1 or 2, 25% (n = 64) with Hunt-Hess grade 3, and 26% (n = 68) with Hunt-Hess grades 4 or 5. One patient (0.4%) had a negative non-contrast head CT scan, 33% (n = 85) had a Fisher grade 2

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Table 1
Characteristics of 259 patients with aneurysmal subarachnoid hemorrhage

	N/Median	%
Age (years)	54	IQR: 45.5–62.50
Sex (female)	197	76%
Smoker	100	45%
Radiographic subarachnoid hemorrhage		
None	1	0.4%
Less than 1 mm	85	33%
More than 1 mm	173	67%
Intraventricular hemorrhage		
None	80	31%
Minimal or one ventricle	106	41%
Two ventricles	62	24%
Casted or pan-ventricular	10	4%
Intraparenchymal hemorrhage		
None	207	80%
Present	51	20%
Hunt-Hess Grade		
1–2	128	49%
3	64	25%
4	54	21%
5	14	5%
Aneurysm location		
Proximal ICA	88	39%
Anterior communicating	61	27%
Pericallosal	6	3%
MCA bifurcation	38	17%
Posterior circulation	33	15%
Treatment		
Clipped	201	78%
Coiled	58	22%

ICA = internal carotid artery, IQR = interquartile range, MCA = middle cerebral artery, N = patient number.

subarachnoid hemorrhage and the remaining 173 patients (67%) had at least 1 mm clot thickness on non-contrast head CT. Fifty-one patients (20%) had intraparenchymal extension. As expected, most patients harbored anterior circulation aneurysms (85%). The majority (78%) of patients were treated with microsurgical clipping.

3.2. Incidence and severity of hyponatremia

Defining hyponatremia as serum sodium ⩽134 mEq, 14% of patients had hyponatremia upon presentation, with 1% of patients displaying severe hyponatremia at initial presentation with serum sodium less than 130 mEq (Fig. 1). Delayed hyponatremia (⩽134 mEq) occurred in 57% of patients and 10% of patients developed delayed severe hyponatremia (⩽130 mEq) (Fig. 1).

For patients with normal serum sodium at presentation, median onset of hyponatremia was 7 days (interquartile range [IQR] 5–9) (Fig. 1). The latest onset occurred at 23 days. The median duration of hyponatremia was 1 day (IQR 1–2). In the setting of treatment for hyponatremia, 69% had hyponatremia lasting for 1 day, 23% for 2 days, and 8% for greater than 2 days.

3.3. Sodium at presentation

Using univariate analysis, sodium at presentation was found to be lower with increasing age, female sex, and in patients with intraparenchymal hematoma (Table 2). Multivariate analysis using these three factors showed a significant association between age and serum sodium at presentation (p = 0.04) (Table 3).

3.4. Hyponatremia

Univariate analysis showed that increasing age was associated with hyponatremia, defined as serum sodium ⩽134 mEq, while higher Hunt-Hess (HH) grade (4 or 5) and aneurysms of the anterior cerebral or anterior communicating arteries were associated with absence of hyponatremia (Table 2). In multivariate analysis of these three variables, only age remained statistically significant (odds ratio [OR] 1.03, p = 0.01) (Table 3).

3.5. Duration of hyponatremia

In univariate analysis, history of smoking, presence of intraventricular hemorrhage, and lower HH grade (1–3) were found to be associated with longer duration of hyponatremia. (Table 2) Using these three variables in the multivariate analysis, smoking history remained significantly associated with an increased duration of hyponatremia (p = 0.02). (Table 3) but intraventricular hemorrhage and HH grade, were no longer significant.

4. Discussion

4.1. Clinical significance of hyponatremia

The significance of hyponatremia in aSAH patients is still a topic of debate. Most institutions target eunatremia in aSAH patients to avoid complications, given the minimal risks and costs of this therapy, especially within the high-risk vasospasm window. Despite maintenance of eunatremia being the standard of care, the importance of hyponatremia remains a controversial topic in aSAH with some authors reporting no association between hyponatremia and mortality, long-term outcome, delayed ischemic neurological deficits (DIND) [6], seizure incidence or neurologic function [3]. However, a recent large meta-analysis by Connolly et al. shows an increased risk of symptomatic vasospasm and several retrospective studies provide evidence that DIND occurs at a higher rate in patients with hyponatremia [7–9]. Zhao et al. presented findings of increased cerebral infarction in patients with high grade aSAH and delayed hyponatremia [10]. In addition, it has been shown that hyponatremia is associated with a longer hospital course, which can lead to secondary complications and increased costs [3,7,9]. With low risk to the patients and recent growing evidence supporting worse outcomes in hyponatremic patients, we continue to recommend treatment of hyponatremia as the standard of care in aSAH patients.

4.2. Incidence of hyponatremia

In our series, hyponatremia occurred at a higher frequency than other contemporary studies (57% vs. 26–50%) [1,3,5]. Compared to the cohort reported by Nakagawa et al., our patients had more severe clinical neurologic injury on presentation with a median HH grade (3 vs. 2) and more subarachnoid blood (67% vs. 54% with Fisher grade 3 or 4) [5]. However, using the Fisher's exact test to compare our results with those of Nakagawa et al., these differences were not statistically significant, suggesting that the baseline characteristics of our patient population are comparable to those in other studies. However, patients in this study underwent daily laboratory evaluation for the first 7 to 10 days following aSAH, or for the duration of their intensive care. Testing frequency is increased to twice a day if the patient is medically complex, such as with polyuria, ventilator-dependence, radiographic vasospasm, or hyponatremia. Testing is increased to four times a day during treatment of hyponatremia. Hypernatremic therapy is initiated only if sodium levels fall below the threshold of eunatremia (Na ⩽134 mEq). Frequent laboratory evaluation of serum sodium at our institution may explain the higher observed incidence of hyponatremia in our study.