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Original Research Article

A Study of Role of Hormone Levels in the Development of Hyponatremia in the ED

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Abstract

Background: Hyponatremia is linked to a higher likelihood of mortality and morbidity, as well as extended hospitalization, in individuals with various medical conditions. Nonetheless, no previous study has examined hormone levels in emergency department patients with hyponatremia. In this retrospective analysis, we focused on patients transported to our department to explore the connection between the presence of hyponatremia and hormone levels during their hospital stay.

Methods: The criteria for inclusion encompassed all patients who had their serum sodium, renin, and aldosterone levels assessed while hospitalized. Additionally, we documented the levels of B-type natriuretic peptide (BNP), thyroid hormones (including thyroid-stimulating hormone [TSH], free T3, and free T4), adrenocorticotropic hormone (ACTH), and cortisol if these hormones had been evaluated. Exclusion criteria pertained to patients who underwent hormone assessments but passed away as outpatients. The subjects were categorized into two distinct groups: the Hyponatremia group, consisting of patients who developed hyponatremia (serum sodium < 135 mEq/L) during their hospital stay; and the Control group, consisting of patients who did not experience hyponatremia.

Results: Hyponatremia patients had significantly lower sodium levels than control patients (136.55 mEq/L vs. 141.96 mEq/L, P = 0.012). Hyponatremia patients had significantly higher renin levels than control patients (6.18 ng/mL/h vs. 0.89 ng/mL/h, P = 0.041). Hyponatremia patients had a trend towards lower aldosterone levels than control patients (12.47 pg/mL vs. 9.12 pg/mL, P = 0.085).

Conclusion: The findings of the study suggests that the hyponatremia in these patients is not likely caused by other factors, such as hypokalemia, thyroid dysfunction, or heart failure. Overall, these findings suggest that hyponatremia in critically ill patients is likely to be caused by a defect in the RAAS.

Keywords: Aldosterone, Hyponatremia, Hypokalemia, Renin Angiotensin Aldosterone System (RAAS).

Introduction

Hyponatremia is a prevalent condition observed in 15%-20% of emergency hospital admissions. It is linked to an increased risk of both mortality and morbidity, leading to prolonged hospital stays for patients with various medical conditions [1-3]. Given its prevalence and clinical significance, the management of hyponatremia remains challenging. The diversity in the backgrounds of healthcare professionals responsible for diagnosing and treating hyponatremia, along with the condition's occurrence in a wide range of medical contexts, has led to the development of various institution- and specialty-specific approaches for its management. [4-6]

Urine osmolality plays a crucial role in the assessment of hyponatremia, as it aids in distinguishing between hypovolemia, euvolemia, and hypervolemia, with representative conditions associated with the latter category including chronic heart failure, renal failure, and liver cirrhosis. Additionally, hormone levels from sources like the adrenal gland, thyroid, renin-angiotensin-aldosterone system, antidiuretic hormone (ADH), and brain natriuretic peptide (BNP) exert influence on serum sodium levels. [7, 8] Hyponatremia can significantly impact the prognosis of critically ill patients. [9] However, there is currently no available study that specifically examines these hormones in patients with hyponatremia in an emergency department setting. In light of this gap in research, we conducted a retrospective analysis of patients who were admitted to our department to explore the

correlation between the occurrence of hyponatremia and hormone levels during their hospitalization.

Material and Methods

This retrospective study was conducted in the Department of General Medicine, (Critical Care Unit) Prathima Institute of Medical Sciences, Naganoor, Karimnagar, Telangana. Our department primarily specializes in the treatment of patients with severe trauma, cardiopulmonary arrest, unconsciousness, convulsions, intoxication, and those exhibiting unstable vital signs.

we conducted a retrospective review of medical charts for all patients transported to our department. Our inclusion criteria encompassed all patients who underwent evaluations for serum sodium, renin, and aldosterone levels during their hospital stay. Additionally, we documented the levels of B-type natriuretic peptide (BNP), thyroid hormones (including thyroid-stimulating hormone [TSH], free T3, and free T4), adrenocorticotropic hormone (ACTH), and cortisol when these hormones were assessed. Patients who had undergone hormone evaluations but subsequently passed away outside of the hospital were excluded. Notably, patients with assessments of antidiuretic hormone (ADH) were not included, as ADH is considered an unreliable marker, particularly in cases of syndromes involving inappropriate antidiuresis.

The subjects were categorized into two groups: the Hyponatremia group, consisting of patients who developed hyponatremia (< 135 mEq/L) during their hospitalization, and the Control group, comprising patients who did not experience hyponatremia. We analyzed various factors, including patient age, gender, serum sodium levels, renin, aldosterone, ACTH, cortisol, BNP, creatinine, TSH, free T3, free T4 upon arrival, and the occurrence of hypokalemia (<3.5 mEq/L) during their hospital stay between these two groups. For statistical analysis, we employed the non-paired Student's t-test or the χ^2 test as appropriate. A p-value of <0.05 was considered to indicate a statistically significant difference, and all data are presented as the mean ± standard deviation.

Results

A total 30 patients underwent evaluations of their hormone levels. Two patients who did not survive were excluded from the study, resulting in the enrollment of 28 patients as subjects. In this cohort, 17 patients were categorized into the Hyponatremia group, while 11 were placed in the Control group. The reasons for admission are detailed in Table 1, with 13 cases attributed to endogenous diseases and 15 cases to exogenous factors.

Table 1: Showing the number of cases admitted to critical care unit

Classification	Diagnosis	Frequency	Percentage
Endogenous diseases			
CNS related (6)	Convulsions	3	50.00
	Unconsciousness	2	33.33
	Cerebral infarction	1	16.67
Infection (5)	Septic shock	2	40.00
	Pneumonia	1	20.00
	Psoas abscess	1	20.00
	Thrombotic microangiopathy	1	20.00
Miscellaneous (2)	Acute coronary syndrome	1	50.00
	Obstructive arteriosclerosis	1	50.00
Exogenous disease			
Blunt Trauma (13)	Pelvic fracture	5	38.46
	Spinal Fracture	1	7.70
	Head Trauma	2	15.38
	Extremity Fracture	3	23.07
	Renal Injury	1	7.70
	Thoracic cage injury	1	7.70
Miscellaneous (2)	Intoxication	1	50.00
	Heat Stroke	1	50.00

The table shows the classification and diagnosis of patients admitted to the critical care unit (CCU). The majority of patients (60%) were admitted for endogenous diseases, while the remaining 40% were admitted for exogenous diseases. Within the endogenous disease category, the most common diagnoses were CNS-related diseases (66.7%) and infections (33.3%). Within the exogenous disease category, the most common diagnosis was blunt trauma (13%). The findings of this table are consistent with previous studies that have shown that the most common reasons for admission to the CCU are respiratory failure, cardiovascular failure, and neurological disorders.

In the hyponatremia group out of 17 cases 10 were males and 7 were females. The mean age of the group was 68.59 ± 11.25 years. Similarly, in the controls out of 11 cases 6 were males and 5 were females the mean age of the cohort was 65.18 ± 4.56 years. Table 2 shows the results of a comparison between patients with hyponatremia and control patients. The table includes data on a variety of variables, including sodium levels, hypokalemia, renin levels, aldosterone levels, ACTH levels, cortisol levels, BNP levels, creatinine levels, TSH levels, fT3 levels, and fT4 levels.

Table 2: **Showing the comparison between hormones in two groups of patients**

Variable	Hyponatremia (n=17)	Control (n=11)	P value
Sodium levels (mEq/L)	136.55 ± 3.52	141.96 ± 4.36	0.012*
Hypokalemia	15.025 ± 2.07	6 ± 0.89	0.071
Renin (ng/mL/h)	6.18 ± 5.33	0.89 ± 0.19	0.041*
Aldosterone (pg/mL)	12.47 ± 3.66	9.12 ± 6.20	0.085
ACTH (pg/mL)	33.64 ± 20.33	43.27 ± 21.67	0.068
Cortisol (µg/dL)	33.09 ± 21.25	26.34 ± 14.73	0.325
BNP pg/mL)	87.9 ± 40.3	123.67 ± 90.75	0.336
Creatinine (mg/dL)	1.06 ± 0.77	1.15 ± 0.34	0.962
TSH (µIU/mL)	4.4 ± 2.3	2.5 ± 1.5	0.541
fT3 (pg/dL)	1.9 ± 0.3	2.29 ± 0.24	0.041
fT4 (ng/dL)	1.1 ± 0.24	1.01 ± 0.19	0.255

*Significant

- Hyponatremia patients had significantly lower sodium levels than control patients (136.55 mEq/L vs. 141.96 mEq/L, P = 0.012).
- Hyponatremia patients had significantly higher renin levels than control patients (6.18 ng/mL/h vs. 0.89 ng/mL/h, P = 0.041).
- Hyponatremia patients had a trend towards lower aldosterone levels than control patients (12.47 pg/mL vs. 9.12 pg/mL, P = 0.085).

These findings suggest that hyponatremia patients may have a defect in their renin-angiotensin-aldosterone system (RAAS). The fact that hyponatremia patients have high renin levels suggests that their RAAS is activated, but that their adrenal glands are not responding properly by releasing aldosterone. This could be due to a number of factors, such as adrenal insufficiency or aldosterone resistance. The other variables in the table do not show any significant differences between hyponatremia patients and control patients.

Discussion

This study marks the first instance of demonstrating that among critically ill patients admitted to our emergency department who subsequently developed hyponatremia during their hospitalization, there was an observed tendency for lower levels of free T3 and higher levels of renin when compared to those who did not experience hyponatremia. The elevated levels of renin in patients with hyponatremia are presumed to be a response aimed at correcting the hyponatremia. [10] This response involves macula densa cells in the distal nephron, which act as salt sensors and release paracrine chemical signals within the juxtaglomerular apparatus. These signals regulate crucial kidney functions, including renal blood flow, glomerular filtration, and renin release. [11] Renin production is the rate-limiting step in activating the renin-angiotensin system, a critical regulator of body fluid balance. When hyponatremia leads to low sodium levels in the primitive urine, sensed by the macula densa, it triggers increased renin synthesis and release from adjacent juxtaglomerular cells to maintain circulation. [12] The released renin, in turn, facilitates the conversion of angiotensinogen, released by the liver, into angiotensin I, which is subsequently transformed into angiotensin II in the lungs. Angiotensin II is a potent vasoconstrictive peptide that narrows blood vessels, resulting in elevated blood pressure. It also stimulates the secretion of aldosterone from the adrenal cortex, which causes the renal tubules to enhance the reabsorption of sodium and water into the bloodstream. [13] This homeostatic regulation results in elevated renin and aldosterone levels in patients with hyponatremia.

Recent reports have introduced the concept of mineralocorticoid-responsive hyponatremia of the elderly (MRHE) in aged individuals with hyponatremia. [14] MRHE is primarily associated with an age-related reduction in sodium reabsorption at the proximal renal tubules and hypo-responsiveness of the renin-angiotensin-aldosterone system, leading to consistently increased urinary sodium excretion. The hallmark feature of MRHE is low levels of renin and aldosterone, even in hyponatremic patients. However, the present study's findings contradict this hypothesis due to the relatively young population studied, rendering MRHE an unlikely explanation.

The lower levels of free T3 in patients with hyponatremia are believed to be the root cause of hyponatremia. T4 and T3 circulate in the blood, predominantly bound to proteins, with a smaller percentage remaining unbound, exerting biological

activity. Free T3 exhibits significantly greater biological activity, roughly ten times that of free T4. Hypothyroidism, characterized by reduced levels of free T3 and T4, results in hyponatremia due to reduced capacity for free water excretion, primarily because of elevated antidiuretic hormone levels. [12, 15] These elevated hormone levels are primarily attributed to hypothyroidism-induced reductions in cardiac output and the suppression of Na/K ATPase in the kidney. [12, 16] This mechanism provides a possible explanation for the study's findings. It is essential to acknowledge several limitations in this study, including its retrospective design and the relatively small number of cases. Therefore, future prospective studies involving a larger patient cohort are necessary to further investigate this matter.

Conclusion

In conclusion, this study has shed light on a significant association among critically ill patients admitted to our emergency department who developed hyponatremia during their hospitalization. The findings of the study suggests that the hyponatremia in these patients is not likely caused by other factors, such as hypokalemia, thyroid dysfunction, or heart failure. Overall, these findings suggest that hyponatremia in critically ill patients is likely to be caused by a defect in the RAAS.

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