

## Relationship between the Occurrence of Hyponatremia and the Hormone Levels in the Emergency Department

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### Original Research Article

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**Abstract:** Hyponatremia is associated with an increased risk of mortality and morbidity and a longer hospital stay in patients presenting with a range of conditions. However, no report has evaluated the hormone levels specifically for patients with hyponatremia in the emergency department. We retrospectively analyzed the patients who were transported to our department to investigate the relationship between the occurrence of hyponatremia and the levels of hormones during hospitalization. From January 2014 to September 2017, a medical chart review was retrospectively performed for all patients who were transported to our department. The inclusion criteria were all patients who underwent an evaluation for the levels of serum sodium, renin and aldosterone during hospitalization. In addition, we noted the levels of BNP, thyroid hormones (thyroid-stimulating hormone [TSH], free T3, free T4), adrenocorticotropic hormone (ACTH) and cortisol during hospitalization if these hormones had been evaluated. The exclusion criteria were patients who had undergone a hormone evaluation but died as outpatients. The subjects were divided into two groups: a Hyponatremia group, including patients who developed hyponatremia (< 135 mEq/L) during hospitalization; and a Control group, including patients who did not develop hyponatremia. The patients' age, sex, levels of serum sodium, renin, aldosterone, ACTH, cortisol, BNP, creatinine, TSH, free T3 and free T4 on arrival and the occurrence of hypokalemia (<3.5 mEq/L) during hospitalization were analyzed between the two groups. During the investigation period, there were 19 patients in the Hyponatremia group and 13 in the Control group. There were no significant differences between the two groups with regard to the age, sex ratio or levels of ACTH, cortisol, BNP, creatinine, TSH or T4. However, the level of renin in the Hyponatremia group was significantly higher than in the Control group, and the level of free T3 in the Hyponatremia group was significantly lower than in the Control group. The levels of aldosterone and the ratio of the occurrence of hypokalemia during hospitalization in the hyponatremia group were greater than in the control group, although not to a significant degree. Among critically ill patients admitted to our emergency department who developed hyponatremia during hospitalization, the levels of free T3 tended to be lower and the levels of renin higher than in those who did not develop hyponatremia.

**Keywords:** Hyponatremia; hormone; emergency department.

## INTRODUCTION

Hyponatremia is a clinical feature in 15%–20% of emergency admissions to the hospital. It is associated with an increased risk of mortality and morbidity and a longer hospital stay in patients presenting with a range of conditions [1-3]. Hyponatremia is therefore both common and important. Nevertheless, the management of such patients remains problematic. The prevalence of hyponatremia under a wide range of conditions and the fact that hyponatremia is managed by clinicians with a

broad variety of backgrounds have fostered diverse institution and specialty-based approaches to its diagnosis and treatment [1-3].

Urine osmolality is used to evaluate hyponatremia, as the urine sodium concentration is useful for differentiating hypovolemia from euvolemia or hypervolemia [1]. Representative diseases of hypervolemia are chronic heart failure, renal failure and liver cirrhosis. The levels of hormones, such as those of

the adrenal gland, thyroid, renin-angiotensin-aldosterone system, antidiuretic hormone (ADH) or brain natriuretic peptide (BNP), influence the serum sodium level [4, 5]. Hyponatremia can affect the prognosis of critically ill patients [6]. However, no report has evaluated such hormones specifically for patients with hyponatremia in the emergency department.

Accordingly, we retrospectively analyzed patients who had been transported to our department to investigate the relationship between the occurrence of hyponatremia and the levels of hormone during hospitalization.

## METHODS

The protocol of this retrospective study was approved by the review board of Juntendo Shizuoka Hospital, and all examinations were conducted according to the standards of good clinical practice and the Declaration of Helsinki.

The Department of Acute Critical Care Medicine, Juntendo Shizuoka Hospital, which is a hospital with 552 beds in the Izu peninsula at Shizuoka prefecture located near Tokyo, serves a population of approximately 270,000. Our department mainly treats patients with severe trauma, cardiopulmonary arrest, unconsciousness, convulsion, intoxication and unstable vital signs.

From January 2014 to September 2017, a medical chart review was retrospectively performed for all patients who were transported to our department. The inclusion criteria were all patients who underwent an evaluation for the levels of serum sodium, renin and aldosterone during hospitalization. In addition, we noted the levels of BNP, thyroid hormones (thyroid-stimulating hormone [TSH], free T3, free T4), adrenocorticotropic hormone (ACTH) and cortisol during hospitalization if these hormones had been evaluated. The exclusion criteria were patients who had undergone a hormone evaluation but died as outpatients. We did not include the patients who had their level of ADH. Because ADH is an unreliable

marker, fluctuating in cases of syndromes of inappropriate antidiuresis [7].

The subjects were divided into two groups: a Hyponatremia group, including patients who developed hyponatremia (< 135 mEq/L) during hospitalization; and a Control group, including patients who did not develop hyponatremia. The patients' age, sex, levels of serum sodium, renin, aldosterone, ACTH, cortisol, BNP, creatinine, TSH, free T3 and free T4 on arrival and the occurrence of hypokalemia (<3.5 mEq/L) during hospitalization were analyzed between the two groups.

Statistical analyses were performed using the non-paired Student's *t*-test, or the  $\chi^2$  test, as appropriate. A *p*-value of <0.05 was considered to indicate a statistically significant difference. All data are presented as the mean  $\pm$  standard deviation.

## RESULTS

During the investigation period, a total of 6380 patients were treated in the emergency room. Among these patients, 36 had their hormone levels evaluated. After excluding 4 patients who did not survive and were therefore not included in the study, 32 patients were enrolled as subjects. There were 19 patients in the Hyponatremia group and 13 in the Control group.

The reasons for admission are shown in Table 1. There were 14 cases of endogenous disease and 17 cases of exogenous disease.

The results of an analysis between the two groups are shown in Table 2. There were no significant differences between the two groups with regard to the age, sex ratio or levels of ACTH, cortisol, BNP, creatinine, TSH or T4. However, the level of renin in the Hyponatremia group was significantly higher than in the Control group, and the level of free T3 in the Hyponatremia group was significantly lower than in the Control group. The levels of aldosterone and the ratio of the occurrence of hypokalemia during hospitalization in the hyponatremia group were greater than in the control group, although not to a significant degree.

**Table-1: Reason for admission**

Endogenous disease		
Classification	Diagnosis	Number
CNS problem		(7)
	Convulsion	3
	Unconsciousness	2
	Cerebral infraction	2
Infection		(6)
	Septic shock	3
	Pneumonia	1
	Psoas abscess	1
	Thrombotic microangiopathy	1
Others		(2)
	Acute coronary syndrome	1
	Obstructive arteriosclerosis	1
Exogenous disease		
Classification	Diagnosis	Number
Blunt trauma		(14)
	Pelvic fracture	6
	Spinal fracture	2
	Head trauma	2
	Extremity fracture	2
	Renal injury	1
	Thoracic cage injury	1
Intoxication		2
Heat stroke		1

**Table-2: Results of the analyses**

	Hyponatremia (n=19)	Control (n=13)	p wave
Sex (male/female)	9/10	7/6	n.s.
Age (years)	69.5 ± 14.4	68.3 ± 20.3	n.s.
Sodium level (mEq/L)	137.1 ± 10.2	142.8 ± 5.0	<0.05
Renin (ng/mL/h)	6.21 ± 12.5	0.7 ± 0.8	<0.05
Aldosterone (pg/mL)	12.3 ± 6.6	9.5 ± 9.2	0.07
ACTH (pg/mL)	34.9 ± 44.3 (n=15)	44.2 ± 52.5 (n=9)	n.s.
Cortisol (µg/dL)	34.3 ± 36.3 (n=17)	25.2 ± 16.7 (n=9)	n.s.
BNP (pg/mL)	88.8 ± 81.1 (n=18)	124.8 ± 108.6 (n=10)	n.s.
Creatinine (mg/dl)	1.05 ± 0.70	1.13 ± 0.65	n.s.
TSH (µIU/mL)	4.4 ± 9.3 (n=17)	2.5 ± 1.6 (n=12)	n.s.
Free T3 (pg/dL)	1.8 ± 0.5 (n=17)	2.3 ± 0.3 (n=11)	<0.05
Free T4 (ng/dL)	1.0 ± 0.2 (n=17)	1.0 ± 0.2 (n=12)	n.s.
Hypokalemia (yes)	16	7	0.06

BNP: brain natriuretic peptide, TSH: thyroid stimulation hormone, n.s.: not significant

**DISCUSSIONS**

This is the first study to demonstrate that, among critically ill patients admitted to our emergency department who developed hyponatremia during hospitalization, the levels of free T3 tended to be lower and the levels of renin higher than in those who did not develop hyponatremia.

The high levels of renin in patients with hyponatremia are thought to be a response to correct the

hyponatremia. Macula densa cells in the distal nephron are salt sensors that generate paracrine chemical signals in the juxtaglomerular apparatus to control vital kidney functions, including the renal blood flow, glomerular filtration and renin release [8]. Renin production is the rate-limiting step in the activation of the renin-angiotensin system, a key modulator of body fluid homeostasis. Hyponatremia followed by low levels of sodium in the primitive urine sensed by the macula densa cause increased renin synthesis and release from

adjacent juxtaglomerular cells to maintain circulation [8]. The released renin then promotes the conversion of angiotensinogen, released by the liver, to angiotensin I, which is subsequently converted to angiotensin II in the lungs. Angiotensin II is a potent vasoconstrictive peptide that causes blood vessels to narrow, resulting in increased blood pressure, and also stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone causes the renal tubules to increase the reabsorption of sodium and water into the blood [9]. Such homeostatic regulation results in high levels of renin and aldosterone in patients with hyponatremia.

Recently, the concept of mineralocorticoid responsive hyponatremia of the elderly (MRHE) has been reported in aged people with hyponatremia [10]. The main mechanism underlying MEHE is the age-related decreased sodium reabsorption at the proximal renal tubules and hypo responsiveness of renin-angiotensin-aldosterone system causing constantly increased urinary sodium excretion. The characteristic findings of MRHE are low levels of renin and aldosterone, even in hyponatremia patients. As the results of the present study are opposite due to the population in our study being relatively young, this hypothesis of MRHE is not true for the present study.

The low levels of free T3 in patients with hyponatremia are thought be the ultimate cause of hyponatremia. T4 and T3 circulate in the blood largely bound to proteins, but a small percentage remains unbound, and this free type exerts activity. Free T3 has a much greater biological activity (about 10-fold) than free T4. Hypothyroidism, which is characterized by reduced levels of free T3 and T4, results in hyponatremia because of the decreased capacity of free water excretion due to the elevated levels of antidiuretic hormone. These elevated levels are mainly attributed to the hypothyroidism-induced decrease in cardiac output, in addition to the suppression of Na/K ATPase in the kidney [11, 12]. This mechanism may explain the results of the present study.

There are several limitations associated with this study, including its retrospective design and the small number of cases. Therefore, future prospective studies involving a greater number of patients are needed to further examine this issue.

## CONCLUSION

Among critically ill patients admitted to our emergency department who developed hyponatremia during hospitalization, the levels of free T3 tended to be lower and the levels of renin higher than in those who did not develop hyponatremia.

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## Conflict of interest

The authors declare that they have no conflicts of interest.

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