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Original Article

Internal Medicine Section

Prevalence and Aetiology of Syndrome of Inappropriate Antidiuretic Hormone in Hyponatraemia: A Cross-sectional Study

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ABSTRACT

Introduction: Hyponatraemia is a frequently occurring electrolyte abnormality. Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is one of the common causes of hyponatraemia. SIADH is a disorder of impaired water excretion caused by the inability to suppress the secretion of Antidiuretic Hormone (ADH). The importance of determining the cause of hyponatraemia as SIADH is not only to seek the aetiology of SIADH but also to treat appropriately.

Aim: To determine the prevalence of SIADH in patients with hyponatraemia and its causes in these patients.

Materials and Methods: A cross-sectional study was conducted in the Department of General Medicine at Jubilee Mission Medical College and Hospital, Thrissur, Kerala, India. The study duration was one year and six months, from December 2014 to June 2016. A total of 100 individuals over the age of 18, who were admitted with serum sodium levels under 135 mEq/L, were chosen. Data on the causes of hyponatraemia and SIADH, laboratory evaluations, and assessments based on SIADH criteria were gathered using a structured proforma. The primary outcome variables included the aetiology of SIADH and the causes of hyponatraemia. Frequency and percentages were used to represent the data. The data were analysed using MS Excel.

Results: Among 100 patients, the maximum number of patients with hyponatraemia were in the 59-78 years age group. Forty-two (42) had severe hyponatraemia (Na < 120 mmol/L). The most common cause of hyponatraemia was drug intake (diuretics + antihypertensives), which constituted 42 (42%) of the total 100 patients, followed by SIADH in 33 (33%) patients. Among the aetiologies of SIADH, cerebrovascular accident was the most common (9/100), followed by pneumonia and Selective Serotonin Reuptake Inhibitors (SSRIs) in five patients each. Among the non neurological symptoms, vomiting was the most common symptom in 28 (28%) patients, followed by lethargy in 15 (15%). Among the neurological symptoms associated with hyponatraemia, confusion was the predominant one seen in 10 (10%) patients, followed by drowsiness in 7 (7%).

Conclusion: SIADH is an important cause of hyponatraemia with a high prevalence. The prevalence of SIADH in hyponatraemic patients was 33%. Among the aetiologies of SIADH, cerebrovascular accident was the most common.

Keywords: Antihypertensive agents, Inappropriate secretion, Morbidity, Salt depletion, Sodium

INTRODUCTION

The most typical electrolyte imbalance in hospitalised patients, occurring in upto 6% of cases, is hyponatraemia [1]. It happens because the complex multisystem physiological mechanisms that typically maintain salt and water balance are disrupted. Mild hyponatraemia is typically asymptomatic, but major neurological problems can develop as a result of cerebral oedema when the reduction in serum sodium is large (125 mmol/L) or acute (48 hours). These problems include non cardiogenic pulmonary oedema, hyponatraemic encephalopathy, seizures, coma, and death [2].

Previous studies contend that, among medical patients, the aetiology of hyponatraemia was a more significant predictive factor than the absolute amount of serum sodium. The treatment of underlying causes of hyponatraemia and re-establishing salt and water balance are the cornerstones of the clinical care of hyponatraemia [3-5]. However, it is notoriously difficult to pinpoint the exact cause of hyponatraemia. One of the most frequent causes of severe hyponatraemia is SIADH [2]. Clinical and biochemical standards based on Bartter's original description are necessary for an accurate diagnosis [6].

According to numerous research studies, the primary aetiologies of SIADH are idiopathic, pulmonary, and Central Nervous System (CNS) causes [7-9]. Because severe hyponatraemia in medical inpatients has a poor prognosis and its aetiology is complex, it is crucial for doctors to conduct an accurate clinical assessment and appropriate biochemical tests, as these results will dictate the course of treatment [7].

Although SIADH is reported as one of the most common causes of hyponatraemia in the literature, very few studies have been conducted to generate evidence regarding its prevalence. Hence, the present study was conducted to assess the prevalence of SIADH in hyponatraemia. The objectives were to determine the aetiology of SIADH, its distribution, and the severity of hyponatraemia in the study population.

MATERIALS AND METHODS

A cross-sectional study was conducted in the Department of General Medicine at Jubilee Mission Medical College and Hospital, Thrissur, Kerala, India. The study duration was one year and six months, from December 2014 to June 2016. The Institutional Ethics Committee (IEC) approved the conduct of the present study (ECR/835/KL/INST/2015/06), and written informed consent was obtained from study participants.

Inclusion criteria: A total of 100 patients admitted with a serum sodium value <135 meq/L and aged over 18 years in the Medicine Department were included in the study.

Exclusion criteria: Patients under 18 years of age and those who were not willing to be admitted or receive further treatment were excluded from the study.

Sample size calculation: According to Babaliche P et al., [2], considering the prevalence of SIADH in hyponatraemia as 40% with a precision of 10% and a 95% confidence interval, the sample size was calculated as follows:

$N=Z^2_{1-\alpha/2}*p*(1-p)/d^2$

Z1-α/2-two tailed probability for 95% confidence interval=1.96

p (%)-prevalence of SIADH=0.4

d (%)-precision or allowable error for severe hyponatraemia=0.1

$N=1.96^2 * 0.4 * (1-0.4) / 0.1^2$

N=92.2

Thus, the total sample size required for the study was 92. To account for a non participation rate, another eight subjects were added. So, the final sample size was 100.

The patients included in the study were admitted with various illnesses and stayed in the hospital for an average of 10 days. The diagnosis of SIADH was based on the following criteria:

Essential criteria:

- Extracellular Fluid (ECF) effective osmolality below 270 mOsm/kg water
- Inappropriate urinary concentration (>100 mOsm/kg)
- Clinical euvolaemia (absence of signs of hypovolaemia and hypervolaemia)
- Increased urinary (Na+) while on a normal salt and water intake
- Absence of adrenal, thyroid, pituitary, or renal insufficiency or diuretic use [10].

Supplemental criteria:

- Abnormal water load test (inability to excrete atleast 90% of 20 mL/kg water load in four hours and/or failure to dilute urinary osmolality to below 100 mOsm/kg)
- Arginine Vasopressin Plasma (AVP) level inappropriately raised relative to plasma osmolality
- No significant correction of plasma (Na+) with volume expansion but improvement after fluid restriction.

The patients were classified based on the severity of hyponatraemia into:

- Mild hyponatraemia: 131-134 meq/L
- Moderate hyponatraemia: 120-130 meq/L
- Severe hyponatraemia: <120 meq/L, as per the hyponatraemia guideline development group [10].

These patients were evaluated for the underlying cause of hyponatraemia, which included a detailed history and physical examination followed by appropriate laboratory investigations. A complete history was taken, assessing symptomatology related to the neurological system, such as confusion, ataxia, seizures, stupor, and non neurological symptoms, such as vomiting, hiccups, postural dizziness, lethargy, and muscle cramps. The intake of medications that might cause hyponatraemia was inquired about, and existing co-morbidities were noted. A complete physical examination was conducted, including assessing the hydration status of the patient and signs of hypovolaemia. The hydration status of the patients was clinically evaluated, considering poor skin turgor, mucous membrane dryness, and sunken eyes as signs of hypovolaemia, and oedema and raised jugular venous pulse as signs of hypervolaemia. Patients without these signs were grouped as euvolemic. Plasma and urine osmolality were also assessed, along with investigation findings and radiological reports. All data were collected using a case report form.

STATISTICAL ANALYSIS

The collected data were entered into MS Excel. Descriptive analysis was performed using the mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Comparisons were made using appropriate statistical tests and represented in tables and figures.

RESULTS

Among the 100 patients, the maximum number of patients with hyponatraemia were in the 59-78 years age group, and males were more common [Table/Fig-1].

Parameters		n (%)
Age (in years) Mean±SD	60±1.2	
Age groups (in years)	19-38	2 (2)
	39-58	17 (17)
	59-78	67 (67)
	Above 78	14 (14)
Gender	Male	54 (54)
	Female	46 (46)
Neurological symptoms	Confusion	10 (10)
	Drowsiness	07 (07)
	Ataxia	02 (02)
	Stupor	02 (02)
	Seizures	06 (06)
Non neurological symptoms	Lethargy	15 (15)
	Hiccups	03 (03)
	Muscle cramps	05 (05)
	Vomiting	28 (28)
	Postural dizziness	01 (01)
Hydration status	Hypovolemic	40 (40)
	Euvolemic	42 (42)
	Hypervolemic	18 (18)
Sodium levels	118±2.81	

[Table/Fig-1]: Baseline parameters of study population (N=100).

Among the non neurological symptoms, vomiting was the most common symptom, seen in 28 (28%) patients, followed by lethargy in 15 (15%) patients. Among the neurological symptoms associated with hyponatraemia, confusion was the predominant symptom, seen in 10% of patients, followed by drowsiness in 7 (7%) patients [Table/Fig-1].

The most common cause of hyponatraemia was drug intake (diuretics+antihypertensives), which was seen in 42 out of 100 patients. SIADH was the cause in 33 (33%) patients [Table/Fig-2]. Among the 100 patients, 20 (20%) had severe hyponatraemia, 38 (38%) had moderate hyponatraemia, and 42 (42%) had mild hyponatraemia [Table/Fig-3].

Among the aetiology of hyponatraemia, salt restriction in the diet (42%) was the most common cause, followed by Diabetes Mellitus (DM) (33%) [Table/Fig-4].

Parameters	n (%)
SIADH in hyponatraemia	33 (33)
Other causes of hyponatraemia	67 (67)
Drugs	42 (42)
Thiazides+ARBS/ACEIS	17
Loop diuretics	12
Thiazides	13
SSRI	05
MAOIS	1
TCAS	3
Psychiatric medication	3
Carbamazepine	4
Dehydration	8 (8)
Chronic liver disease	7 (7)
Congestive cardiac failure	4 (4)
Hypothyroidism	3 (3)
Renal failure	2 (2)
Adrenal insufficiency	1 (1)

[Table/Fig-2]: Incidence of SIADH in hyponatraemia (N=100).
ARBS/ACEIS: Angiotensin receptor blockers/ACE inhibitors; SSRI: Selective serotonin reuptake inhibitors; MAOIS: Monoamine oxidase inhibitoes; TCA: Tricyclic antidepressant

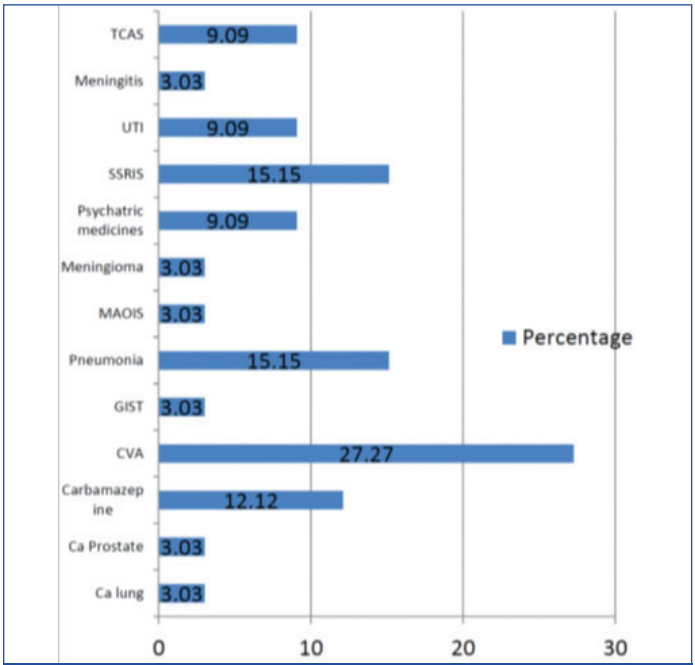
SIADH and severity of hyponatraemia	n (%)
<120 mEq/L	20 (20)
120-130 mEq/L	38 (38)
131-134 mEq/L	42 (42)

[Table/Fig-3]: Distribution of SIADH and severity of hyponatraemia.

Aetiology	n (%)
Salt restriction in diet	42 (42)
Cardiac disease	25 (25)
Cerebrovascular accident	9 (9)
Chronic liver disease	23 (23)
Chronic kidney disease	14 (14)
Hypertension	26 (26)
Diabetes mellitus	33 (33)

[Table/Fig-4]: Aetiology of hyponatermia among study population (N=100).

Among the aetiologies of SIADH (33), cerebrovascular accident was the most common (9 out of 100 patients), followed by pneumonia and SSRIs, each seen in five patients [Table/Fig-5].



[Table/Fig-5]: Aetiology of SIADH (N=33).
TCAS: Tricyclic antidepressants; UTI: Urinary tract infection; SSRI: Selective serotonin reuptake inhibitors; MAOIS: Monoamine oxidase inhibitoes; GIST: Gastrointestinal stromal tumour; CVA: Cerebrovascular accident

Individuals with severe hyponatraemia (serum sodium <120) were the only ones who had disorientation as a presenting symptom. Among the 7% of patients who reported being sleepy, 5% had severe hyponatraemia. Both of the stupor patients exhibited severe hyponatraemia. Six individuals suffered seizures, and five of them had severe hyponatraemia [Table/Fig-6].

Neurological symptoms	Mild n (%)	Moderate n (%)	Severe n (%)	p-value
Confusion	0	0	10 (10)	0.0001
Drowsiness	0	2 (2)	5 (5)	0.199
Ataxia	1 (1)	0	1 (1)	0.422
Stupor	0	0	2 (2)	0.244
Seizures	0	1 (1)	5 (5)	0.098

[Table/Fig-6]: Neurological symptoms and severity of hyponatraemia (N=100).
Domain frequency percentage

DISCUSSION

The current study in Kerala showed that SIADH in hyponatraemia was 33%. Patients with hyponatraemia were more prevalent in the 59-78 years age range. A study by Agarwal SM and Agrawal A at JIPMER and NIMHANS reported a mean age of 48.1±16.1 years for 70 consecutive patients with blood sodium ≤125 mmol/L at presentation or during hospital stay [11]. This finding was consistent with the present study's findings. Another study by Padhi R et al., at the Institute of Medical Sciences and SUM Hospital in Bhubaneswar, Odisha, found a mean age of 60.4±17.2 years [12]. A study on the clinico-aetiological profile and outcome of hyponatraemia in hospitalised adult patients at Kamalnayan Bajaj Hospital, Aurangabad, also reported a similar age range [13].

In the present study, out of a total of 100 patients, 54 were men and 46 were women, indicating that men were more likely to have hyponatraemia than women. This slight increase in male incidence was not considered significant, as the hospital population generally has a higher ratio of males to females.

Among the 100 patients, 42 (42%) had severe hyponatraemia, the highest percentage in the group. Thirty-eight patients (38%) had moderate hyponatraemia, and 20 patients (20%) had mild hyponatraemia. A study conducted in a tertiary care hospital's medical ward from March 2010 to April 2011 reported that 2.4% of patients had severe hyponatraemia (Na <120 meq/L) [14]. The age range of the majority of patients with severe hyponatraemia in that study was 59 to 78 years. A significant number of individuals older than 78 also had severe hyponatraemia (10 out of 14) [14]. In the present study, diuretics and antihypertensives were the most frequent causes of hyponatraemia, accounting for 42 out of every 100 patients. Among the 100 patients, 33% developed SIADH. The most common cause of SIADH in the study was cerebrovascular accident, considered as a co-morbidity. Pneumonia was the second most common cause of SIADH, considered as the primary disease. Thiazides combined with angiotensin receptor blockers or angiotensin-converting enzyme inhibitors accounted for the majority of prescriptions (17%). Other causes of hyponatraemia included dehydration, chronic liver disease, congestive cardiac failure, hypothyroidism, renal failure, adrenal insufficiency, and the use of diuretics and antihypertensives. Diuretics are a significant contributor to hyponatraemia due to their widespread use [15-17].

A total of 25 (50%) patients in the study were on diuretics, which was the most common cause of hyponatraemia according to a study of hyponatraemia in adult hospital inpatients at Al-Diwania Teaching Hospital [18]. Sixteen patients (32%) had heart failure. In another study at Sreebalaji Medical College in Chennai, 24 out of 100 patients developed SIADH (24%), which was the most common cause of hyponatraemia [19]. Robertson GL studied hyponatraemia in patients with spontaneous intracerebral haemorrhage and found that drugs, especially diuretics like furosemide and hydrochlorothiazide, contributed significantly to the cause of hyponatraemia [9]. A study at Kamalnayan Bajaj Hospital in Aurangabad from August 2013 to August 2014 also reported that diuretics (53%) were the most common aetiological factor of hyponatraemia [13].

Out of the 100 patients, 58 individuals were using medications that caused hyponatraemia. The most common medications causing hyponatraemia were thiazides combined with ACEIs/ARBs, loop diuretics, thiazides alone, SSRIs, TCAs, carbamazepine, psychiatric medications, and MAOIs. Caution should be exercised when administering diuretics due to their known harmful side-effects, including hyponatraemia. Hyponatraemia is also attributed to ARBs/ACEIs. The incidence of hyponatraemia caused by various antihypertensives is rising with the increased use of these medications. In this study, only combinations of medications and diuretics were identified as the culprits behind hyponatraemia. Many patients in the study followed a self-imposed salt restriction in their diet as part of hypertension control.

Confusion was the most common neurological symptom of hyponatraemia, occurring in 10% of patients, followed by sleepiness in 7% of cases. Ataxia, stupor, and seizures were among the other

typical neurological symptoms [20]. In this study, individuals with severe hyponatraemia (serum sodium <120) were the only ones who had disorientation as a presenting symptom. 5% of the 7% of patients who reported being sleepy had severe hyponatraemia. Both of the stupor patients exhibited severe hyponatraemia. Six individuals suffered seizures, and five of them had severe hyponatraemia. In a study of the clinico-etiological profile and outcomes of hyponatraemia in hospitalised adult patients at Kamalnayan Bajaj Hospital in Aurangabad, 76 patients were studied. It was determined that nausea (54%) was the most common gastrointestinal symptom and drowsiness (42%) was the most common neurological symptom. Hypertension (26% of patients) was the most prevalent ailment, followed by diabetes mellitus (33%), cardiac disease (25%), cerebrovascular accident (18%), chronic kidney disease (14%), chronic liver disease (7%), and hypothyroidism (7%), among other frequent conditions. Another study by Natkunam A et al., found that older people with concomitant disorders like cardiac, renal, or hepatic failure were more susceptible to hyponatraemia [21]. The most common co-morbid disorders in the study at Kamalnayan Bajaj Hospital were hypertension (51%) and diabetes mellitus (42%). A study conducted in Istanbul, Turkey, examined the relationship between the severity of hyponatraemia and co-morbidity in elderly patients who develop hyponatraemia [22]. The clinical implication of the current study was that the findings will aid physicians in prioritising the cause of SIADH for effective management.

Limitation(s)

This was a single-centre study, so there was no diversity in the included study population. As a cross-sectional study, follow-ups were not conducted.

CONCLUSION(S)

SIADH is an important cause of hyponatraemia with a high prevalence. Among the aetiology of SIADH, cerebrovascular accidents are the most common, followed by pneumonia and the use of SSRIs. Tracing out SIADH as a cause of hyponatraemia, after excluding other causes, can be a difficult task but it is worth it as it can unmask and treat many correctable causes of hyponatraemia.

REFERENCES

[1] Bhasin Chhabra B, Veitla V, Weinberg S, Koratala A. Demystifying hyponatremia: A clinical guide to evaluation and management. Nutr Clin Prac. 2022;37(5):1023-32.
[2] Babaliche P, Madnani S, Kamat S. Clinical profile of patients admitted with hyponatremia in the medical intensive care unit. Indian J Crit Care Med. 2017;21(12):819-24.
[3] Liamis G, Megapanou E, Elisaf M, Milionis H. Hyponatremia-inducing drugs. Front Horm Res. 2019;52:167-77.
[4] Rodenburg EM, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, et al. Thiazide-associated hyponatremia: A population-based study. Am J Kidney Dis. 2013;62(1):67-72.
[5] De las Peñas R, Ponce S, Henao F, Camps Herrero C, Carcereny E, Escobar Álvarez Y. SIADH-related hyponatremia in hospital day care units: Clinical experience and management with tolvaptan. Support Care in Cancer. 2016;24:499-507.
[6] Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. Endocrinol Metab Clin North Am. 2003;32(2):459-81.
[7] Burst V. Etiology and epidemiology of hyponatremia. Front Horm Res. 2019;52:24-35.
[8] Chow KM, Kwan BC, Szeto CC. Clinical studies of thiazide-induced hyponatremia. J Natl Med Assoc. 2004;96(10):1305-08.
[9] Robertson GL. Disorders of the Neurohypophysis. In: Harrison's Principles of Internal Medicine, Kasper DL, Jameson J, Fauci AS, , Hauser SL, Longo DL, Loscalzo J. eds. , 17th edition volume 11 2222. McGraw Hill; 2018.
[10] Verbalis, JG. In Diseases of the Kidney Schrier RW, Gottschalk CW eds. 6th ed, 2400. Boston: Little Brown. 1997.
[11] Agarwal SM, Agrawal A. A comparative study of the clinicoetiological profile of hyponatremia at presentation with that developing in the hospital. Indian J Med Res. 2011;134(1):118-22.
[12] Padhi R, Panda BN, Jagati S, Patra SC. Hyponatremia in critically ill patients. Indian J Crit Care Med. 2014;18(2):83-87.
[13] Baji PP, Borkar SS. Clinicoetiological profile and outcome of hyponatremia in hospitalised adult patients. Int J Sci Rep. 2015;1(7):293-98.
[14] Chatterjee N, Sengupta N, Das C, Chowdhuri AR, Basu AK, Pal SK. A descriptive study of hyponatremia in a tertiary care hospital of Eastern India. Indian J Endocrinol Metab. 2012;16(2):288-91.
[15] Schrier RW. Body water homeostasis: Clinical disorders of urinary dilution and concentration. J Am Soc Nephrol. 2006;17(7):1820-32.
[16] Bal C, Gompelmann D, Krebs M, Antoniewicz L, Guttmann-Ducke C, Lehmann A, et al. Acute symptomatic hyponatremia in setting of SIADH as an isolated presentation of COVID-19. IDCases. 2020;21:e00859.
[17] Bal C, Gompelmann D, Krebs M, Antoniewicz L, Guttmann-Ducke C, Lehmann A, et al. Associations of hyponatremia and SIADH with increased mortality, young age and infection parameters in patients with tuberculosis. Plos one. 2022;17(10):e0275827.
[18] AL-Barqawi ARH. A study of hyponatremia in hospitalized patients. QMJ. 2007;3(4):112-14.
[19] Padma V, Javid SM, Narendran, Anand NN. Study of symptomatic hyponatremia in elderly patients. Int J Pharm Bio Sci. 2016;7(2)B:434-40.
[20] Hunnur M, Bhat R, Bhat KR, Kannan V, Kavitha VP. A prospective study of SIADH in hospitalised patients. Journal of the Association of Physicians of India. 2001;49:0004-5772.
[21] Natkunam A, Shek CC, Swaminathan R. Hyponatremia in a hospital population. J Med. 1991;22(2):83-96.
[22] Kayar NB, Kayar Y, Ekinci I, Erdem ED, Ismailova M, Sit D. Relation between severity of hyponatremia and comorbidity in elderly patients who develop hyponatremia. Bio Med. 2016;27(3):872-76.

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