

Original Research Article

Syndrome of inappropriate antidiuretic hormone secretion and cerebral salt wasting as the common causes of hyponatremia in tertiary care hospital

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ABSTRACT

Background: Hyponatremia is a typical condition of electrolyte disturbance that may be euvolemic, hypovolemic or hypervolemic. Proper interpretation through laboratory tests helps to differentiate the types and causes of hyponatremia. This study was conducted to evaluate the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW) as the common causes of hyponatremia in tertiary care hospital.

Methods: A prospective interventional study was conducted, including hyponatremia cases, admitted in NTU/ICU/CCU and other medical wards at Ruby Hall Clinic from August 2011 to December 2013.

Results: Of 150 patients enrolled in this study, 33.33% patients were euvolemic, 34% patients were hypervolemic and 32.66% patients were hypovolemic. For the euvolemic patients, SIADH (68%) was the most common cause; whereas, CSW (34.39%) was the common cause for hypovolemic type of hyponatremia. Stroke was found to be the most common cause of SIADH (55.88%), Intra-cerebral bleeding was observed to be the most common causative factor between SIADH and CSW associated hyponatremia.

Conclusions: Hyponatremia in central nervous system disorder patients frequently occurred due to SIADH and CSW. Most common cause of SIADH was stroke and for CSW it was intra cerebral bleed.

Keywords: Euvolemic, Hyponatremia, Hypervolemic, Hypovolemic, Intra-cerebral bleeding, Stroke

INTRODUCTION

Hyponatremia is a common electrolyte disorder characterized by syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting (CSW). Hyponatremia is increasingly noticed in hospitalized especially in intensive care units and nursing home patients with mortality and morbidity rate ranging from 5-50%.^{1,2} Health care setting and patient population type has a crucial role in its prevalence and occurrence is independent of sex and age.³

Hyponatremia is commonly observed in elderly patients especially with comorbidities such as cardiac, hepatic or renal failure.⁴ Usually, most of the patients notice

symptoms such as anorexia, nausea, vomiting, headache and irritability. However, patients with serum sodium concentration greater than 130 mEq/L are usually asymptomatic.⁵ Hyponatremia can be associated with low, normal, or high tonicity. It occurs due to inability of the kidney to excrete water load or excess water intake, most often due to an inability to suppress anti-diuretic hormone (ADH) secretion.⁶ However, hyponatremia is not a homogenous disorder and depending upon the volume status of the patient it can either be euvolemic, hypervolemic or hypovolemic.⁷

The two major causes of hyponatremia; SIADH and CSW are difficult to distinguish; although it is very important to know the cause of hyponatremia since the

treatments are very different. The major clinical differences in SIADH and CSW are fluid status in patient and urine output that is higher in CSW than in patients with SIADH.⁸ Patients with CSW are hypovolemic compared to euvoletic or hypervolemic in patients with SIADH.⁹ In cases with CSW, treatment approaches used are fluid restoration and treating the primary subarachnoid hemorrhage and aneurysm.^{8,10}

On the other hand, patients with SIADH are treated with fluid restriction and reducing body fluid volume with hypertonic saline, or vasopressin inhibitors such as demeclocycline and/or diuretics including furosemide.¹¹

There are very few Indian studies investigating the different profiles of hyponatremia. Therefore, this study was done to have an understanding on different profiles of hyponatremia and their presentation in tertiary care setting. Furthermore, causes of SIADH and CSW were also identified.

METHODS

This prospective interventional study was conducted at Ruby Hall Clinic from August 2011 to December 2013. All cases of hyponatremia admitted in NTU/ICU/CCU and other medical wards of the hospital were enrolled. The study protocol was approved by the Institutional Ethics Committee and was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Written informed consent was obtained from each participant before carrying out any study related procedure.

Inclusion criteria

Patients developing hyponatremia with serum sodium level <130 mmol/L within first 4 days of their admission were enrolled. Hyponatremia was classified as mild, moderate, severe and critical (Table 1).

Table 1: Classification of hyponatremia.

Severity	Sodium levels (mmol/L)
Mild hyponatremia	130-120
Moderate hyponatremia	120-110
Severe hyponatremia	110-100
Critical hyponatremia	<100

Patient’s clinical picture will be correlated with level of hyponatremia and clinical picture after correction will be studied and also other factors affecting clinical picture will be noted.

Exclusion criteria

Patients who developed hyponatremia after 4 days of hospital admission were excluded from the study.

Data collection

Patients satisfying the inclusion criteria were selected randomly and information was recorded about the patient demographics, details of admission, disease status of patient, past significant medical history, drug history, other significant medical history, physical examination, laboratory investigation, diagnosis, therapy used and follow up of patients.

RESULTS

These results are in continuation to those reported in our previous publications. In total, 150 patients were enrolled in this prospective observational study. Majority of the patients were above 50 years of age (60.7%) while; 57.3% of this population were men. All the hyponatremia cases were divided into three groups depending on the type; either euvoletic, hypovolemic or hypervolemic type. Patients with hypervolemic type were highest (34%) followed by euvoletic (33.3%) and hypovolemic (32.7%) (Table 2).

Table 2: Types of hyponatremia cases according to volume status.

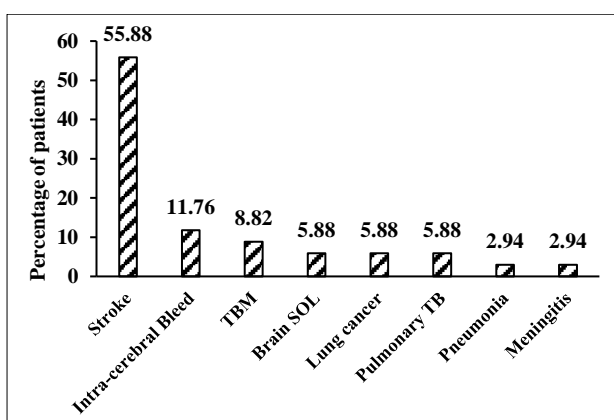
Type of hyponatremia n (%)	Number of patients N= 150
Euvoletic	50 (33.3)
Hypervolemic	51(34.0)
Hypovolemic	49 (32.7)
Data is presented as n%.	

This study showed 50 euvoletic patients, of which 34 patients showed SIADH as the causative factor, 13 patients had low intake of sodium and 3 had hypothyroidism. Patients with euvoletic hyponatremia were having normal central venous pressure (CVP), serum natriuretic peptides and urine output. Patients showed absence of edema and signs of dehydration but had mild increase in urine sodium.

Patients with hypervolemic hyponatremia having edema, raised/normal CVP with increased total body water and total body sodium concentration were observed in 51 patients. The causes of such hypervolemic hyponatremia were acute renal failure in seven patients, chronic kidney diseases in 13, congestive cardiac failure in 16, cirrhosis in 13 and sepsis in two patients.

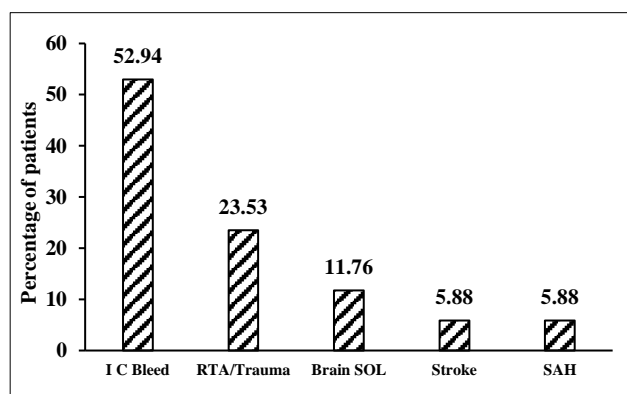
Patients with hypovolemic type of hyponatremia was observed in 49 patients; of which 17 were due to CSW, 12 patients due to vomiting and diarrhea, 10 were due to excess diuresis, nine due to trauma/blood loss and one patient had pancreatitis. Patients with hypovolemic type of hyponatremia showed no edema, signs of dehydration, low CVP, decreased urine output, increased in case of CSW and diuretic excess.

Syndrome of inappropriate antidiuretic hormone was reported to be most common cause of hyponatremia, in 34 patients (22.67%). Patients generally had no edema, no signs of dehydration, blood urea, serum uric acid, serum potassium and serum natriuretic peptides were all normal. Patients also had decreased or normal urine output and hematocrit, mild increased urine sodium and normal or high CVP. Etiology of SIADH secretion was due to multiple causes affecting various systems of body. Stroke was found to be the most common cause of SIADH (55.88%), followed by intra-cerebral bleeding in four patients (11.76%), Tuberculous meningitis in three patients (8.82%), lung cancer in two patients (5.88%), pulmonary tuberculosis and space-occupied lesion (SOL) of the brain or post-surgery in two patients while pneumonia and meningitis were seen in one patient (2.94 %) each (Figure 1).



SOL, space occupied lesion; TB, tuberculosis; TBM, tuberculosis

Figure 1: Causes of SIADH in patients with hyponatremia.



IC, intra-cerebral; RTA, renal tubular acidosis; SAH, subarachnoid hemorrhage; SOL, space occupied lesion; TB, tuberculosis; TBM, tuberculosis meningitis.

Figure 2: Causes of CSW in patients with hyponatremia.

This study showed 17 patients with CSW, among which nine patients (52.94%) had CSW due to intra-cerebral bleed, followed by four patients (23.53%) due to renal tubular acidosis/trauma. Brain SOL/post-surgery was

responsible for CSW in two patients (11.76%). One patient each (5.88%) showed CSW due to stroke and subarachnoid hemorrhage (Figure 2). All these patients had decreased CVP and serum uric acid, increased urine output, blood urea, urine sodium, hematocrit and serum natriuretic peptides. Patients also showed signs of dehydration and high or normal serum potassium.

DISCUSSION

The underlying mechanisms responsible for development of hyponatremia are SIADH and CSW that are associated with several clinical conditions. Expert panel of hyponatremia guidelines 2007 suggest that SIADH may be associated with tumors, central nervous system (CNS) disorders, pulmonary diseases or induced by drugs such as antipsychotic agents, antidepressants, anticonvulsants, angiotensin-converting enzyme (ACE) inhibitors, 3,4-Methylenedioxy methamphetamine (MDMA), and oxytocin; thus, causing neurological disturbances.^{12,13} This study determines different hyponatremia profile and investigated the causes of SIADH and CSW.

The key findings from this study indicate preponderance of men above 50 years of age. There was a modest difference between the percentage of patients with hypervolemia, hypovolemia and euvolemia; however, majority of patients showed hypervolemia followed by euvolemia and hypovolemia. Hypervolemia was due to SIADH caused majorly by liver, kidney and heart diseases, while hypovolemia caused by CSW was mainly due to vomiting, diarrhea, diuresis and trauma wherein blood or fluid loss occurred.

In previous publication it was demonstrated that hyponatremia is highly prevalent; especially, the elderly patients are the major victims. Vurgese et al, and Anderson et al, also reported findings in similar type of population.^{14,15} Previous Indian studies have also reported similar men preponderance above 50 years of age.^{6,16} In contrast, few investigations showed that women are generally affected more by hyponatremia than men (52-70%).¹⁷⁻¹⁹ The present study revealed 39.3% of study population aged below 50 years. This suggests, though hyponatremia is more prevalent in age above 50 years, it can impact younger patients too.

This study enrolled almost equivalent number of different types of patients with hyponatremia. patients with euvolemic were 33.3%, hypervolemic, 34.0% and hypovolemic hyponatremia were 32.7%. Other reported hospital-based studies have found euvolemic hyponatremia as the commonest type.⁶ A study reported by Mittal et al, showed highest number of patients with euvolemia (61.6%) and least patients with hypovolemia (17.2%), similar to the present study. They reported CNS infections, chronic liver disease and acute gastroenteritis as the common causes of hyponatremia in hospitalized patients and presented with intracranial hemorrhages as seen in this study.^{6,16} Although clearly not indicative of

the overall prevalence of hyponatremia globally, it has been observed in as high as 42.6% of patients in a large acute care hospital in Singapore and in 30% of patients hospitalized in an acute care setting in Rotterdam.^{5,20,21}

The most common cause of hyponatremia in the present study was SIADH that was in accordance with the reported studies. In their study, Padhi et al, reported 36.2% of patients with SIADH. They also reported severe sepsis (21.5%) and trauma (21.1%) as the most common cause of hyponatremia.²² In a study by Rao et al, the most common cause was SIADH (30.0%) and the other factors were medications (24.0%) and renal losses (21.0%), respectively.²³

In this study, stroke was found to be the most common cause of SIADH in 19 cases (55.88%), followed by intracerebral bleeding, tuberculous meningitis, lung cancer, pulmonary tuberculosis, brain SOL/post-surgery, pneumonia and meningitis were few other causes of SIADH. Likewise, in a prospective study of 1000 patients with stroke were evaluated for hyponatremia and it was observed that among them 67% patients had SIADH and 33% had CSW. The majority of patients with SIADH had ischemic stroke compared to patients with CSW that was in accordance with this study.²⁴

High levels of neurohormone, arginine vasopressin (AVP) is the trademark feature of SIADH. Arginine vasopressin exerts its action by binding to V2 receptors in the collecting ducts of the kidneys, causing free water to be reabsorbed into the body instead of allowing to be excreted in through urine. It regulates body's water-sodium balance; nevertheless, its abnormal secretion results in water retention that has a dilutional effect on sodium concentration in the plasma, resulting in hyponatremia.^{25,26}

Another common cause of hyponatremia reported in this study was CSW. In this study CSW was due to intracerebral bleed seen in 52.94% followed by renal tubular acidosis or trauma, brain SOL/post-surgery, stroke and subarachnoid hemorrhage. The factors that play a major role in CSW are the natriuretic factors such as an atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide, and possibly dendroaspis natriuretic peptide.

These peptides are believed to be secreted in injury or trauma. Other mechanisms suggest that downregulation of renal sodium transporters due to extracellular volume expansion and the adrenergic surge that occurs in the early phase of brain injury might cause pressure natriuresis. Making the distinction between CSW and SIADH is important because the treatment for the two conditions is very different.^{27,28}

This study was limited by single center, single arm and small sample size; hence it would not be appropriate to extrapolate the results to a large population.

CONCLUSION

Hyponatremia in CNS disorder patients frequently occurs due to SIADH and CSW. Most common cause of SIADH was stroke and for CSW it was intra cranial bleed. They are differentiated by volume status, urine sodium, CVP, urine output, blood urea. Larger randomized controlled trial are required to validate the outcomes.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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