

Original Research Article

Aetiological evaluation of hyponatremia in hospitalised patients and its prognostic implication in disease outcome

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ABSTRACT

Background: Hyponatremia is very common in clinical practice. Proper evaluation of hyponatremia is essential as causes are many and management of it depends on the aetiology and its long-term outcome. Aetiological evaluation of hyponatremia in hospitalised patients and its prognostic implication in disease outcome was undertaken as such studies were rare in this zone.

Methods: One hundred patients whose serum sodium level was <135 mEq/L were studied. The serum sodium and osmolality and urinary sodium and osmolality were estimated in all. The degree of hyponatremia, outcome after treatment and duration of hospital stay were analysed.

Results: The mean age was 60.5 years. There were 73% males and 27% females. The incidence of hyponatremia was 10.7%. The mean serum sodium was 129.96 mEq/L and urinary sodium was 40.3 mEq/L while the mean serum osmolality was 272.8 mOsm/kg and urinary osmolality was 357.7 mOsm/kg. Euvolemia, hypervolemia and hypovolemia were observed in 51%, 28% and 21% respectively. The common clinical features were drowsiness (22%), disorientation (20%), fever (28%), nausea (24%), anorexia (15%), vomiting (14%), hiccup (10%). The common causes were SIADH (34%), renal causes (15%), sepsis (13%), endocrinopathy (11%) and diuretics (11%). The common comorbidities were hypertension (66%) and diabetes mellitus (41%). The mortality was 7%. No side effect was observed during management of hyponatremia.

Conclusions: Proper management of hyponatremia irrespective of aetiology had a better prognosis. Factors which are modifiable should be searched and rectified.

Keywords: Aetiology, Clinical features, Hyponatremia, Outcome

INTRODUCTION

The incidence of hyponatremia is increasing day by day due to emerging incidence of various diseases and their management by various drugs. When serum sodium level falls below 135 mEq/L, it is called hyponatremia and it

may be mild when serum sodium level is 130-134 mEq/L, moderate when serum sodium level is 120-129 mEq/L and severe when serum sodium level is <120 mEq/L.¹⁻³ The prevalence of hyponatraemia ranges from 1-40% in different studies.⁴⁻⁵ The incidence of mild hyponatremia is up to 30-42%.⁴

The prevalence of severe hyponatremia e.g. serum sodium level <125 mEq/L is 2-3%.^{4,6} Basing on the volume status, the hyponatremia may be hypovolemic, euvolemic or hypervolemic.^{7,8} The causes of hypovolemic hyponatremia are (a) renal-salt losing nephropathies (reflux nephropathy, post-obstructive nephropathy, interstitial nephropathies, medullary cystic disease and recovery phase of acute tubular necrosis), thiazide diuretics, cerebral salt wasting syndrome, (b) non-renal-vomiting, diarrhoea, tube drainage, sweating and burns.

The causes of euvolemic hyponatremia are polydipsia, hypothyroidism, hypopituitarism, primary adrenal insufficiency, beer potomania, stress, drugs. The causes of hypervolemic hyponatremia are cirrhosis of liver, nephrotic syndrome, congestive heart failure (CHF) and acute kidney injury and chronic kidney disease. Many of the hyponatremic patients are asymptomatic. The clinical features are usually nonspecific e.g. headache, lethargy, anorexia.⁹ However, in severe hyponatremia anorexia, nausea, vomiting, headache, irritability to attend sensorium, lethargy, seizures and coma are prominent features.¹⁰ In severe form, it may cause brainstem herniation leading to pulmonary oedema, hypoxia and respiratory arrest.¹¹ When symptoms are associated with sepsis and respiratory failure in hospitalized patients, the prognosis is usually poor.¹²

In acute hyponatremia, which develops within 48 hours, the patients are symptomatic even when serum sodium level is above 120 mEq/L, whereas patients may have less symptoms or remain asymptomatic even though serum sodium level is less than 110 mEq/L in chronic hyponatremia which develops over several days or weeks. This is so because in acute hyponatremia brain gets less time for adaptation. The common causes of acute hyponatremia are post-operative states where hypotonic fluids are administered to the patients, accidental ingestion of excessive water, psychogenic polydipsia, thiazide diuretics, gastro-intestinal fluid loss, TURP (transurethral prostatectomy), causes of SIADH, administering multiple tap water enemas etc.

Hyponatremia is diagnosed when serum sodium level is <135 mEq/L. A detailed history, physical examination and appropriate laboratory parameters are essential in order to find out the underlying aetiology. Serum osmolality is normal or increased in pseudohyponatremia whereas it is low in true hyponatremia. Pseudohyponatremia is easily diagnosed by estimating blood sugar, total protein and its fractions and lipid profile. The urinary sodium is <20 mEq/L in hypovolemic and hypervolemic hyponatremia. Urine osmolality is >100 mosm/L in SIADH whereas it is <100 mosm/L in psychogenic polydipsia as well as beer potomania. The criteria which guides the managements of hyponatremia are (a) presence of symptoms, (b) degree of hyponatremia (c) acute (duration <48 hours) or chronic (d) presence of hypotension. Isotonic saline is used to treat hypotension

due to volume depletion. In acute severe hyponatremia, the correction is usually done with hypertonic saline (3% NaCl) at a rate of 1 to 2 mmol/L per hour. Precaution should be taken not to correct up to normal or hypertonic level during first 48 hours.¹³⁻¹⁵

Management of chronic hyponatremia is not urgent, and the cause is to be found out and its removal is enough.¹⁶ Fluid restriction is often the main treatment. Rapid correction of hyponatremia produces central pontine myelinolysis.^{16,17}

The mortality and morbidity rates in acute or symptomatic patients with hyponatremia are high. The mortality is 28% when serum sodium level is <125 mEq/L whereas it is only 9% in eunatremia.¹⁷ The mortality is high when underlying diseases like liver diseases, congestive heart failure or small cell carcinoma of lung are present.¹⁸ The mortality rate of acute symptomatic hyponatremia ranges from 5% to 55%.¹⁹ The mortality in chronic hyponatremic ranges from 14% to 27%.²⁰

Hyponatremia is very common in hospitalized patients and is an indicator of severe disease. As there are many causes of hyponatremia and management depends on the aetiology proper evaluation of hyponatremia is very important. The present study, "Aetiologic evaluation of hyponatremia in hospitalized patients and its implication in disease outcome" is undertaken as such studies are in this zone.

METHODS

After approval of the Institutional Ethics Committee of IMS and Sum Hospital, Bhubaneswar, Odisha and obtaining the informed consent of the patient, the present prospective study was carried out. Patients with age above 15 years and whose serum sodium level was <135 mEq/L were only included. Total 931 patients were screened during the study period and out of them 100 cases (96 had serum sodium level <135 mEq/L at admission and 4 had developed hyponatremia during hospital study) were selected.

The study protocol included a detailed clinical history and thorough physical examination of each patient in the ward. The presenting symptoms, course of symptomatology, the events occurred prior to hospital admission, drug history and presence of co-morbidity illness were recorded. Presence of peripheral and pulmonary oedema, ascites, pleural effusion indicates hypervolemic hyponatremia, while presence of dry tongue, decreased skin turgor, orthostatic hypotension points the hypovolemic state. Complete hemogram, ESR, plasma sugar, blood urea, serum creatinine, serum electrolytes (sodium, potassium, chloride, bicarbonates, phosphates, calcium), routine urine examination, X-ray chest and ultrasonography were performed in all patients. MRI brain, CT head, thyroid function and cortisol

estimation was done on some patients depending on the clinical suspicious. Patients with hyperproteinemia/hypertriglyceridemia, hyperglycemia were excluded.

Blood (3 ml) was collected by venepuncture into an evacuated tube without any anticoagulant. The tubes were centrifuged unopened and the plasma or serum was separated. The serum was analysed for electrolytes, urea and sugar. Urine was collected in a clean container free of any chemicals after sterilizing the bottles.

Determination of serum and urinary sodium: serum and urinary sodium were assessed by ion selective electrode (ISE) method. Determination of serum and urinary osmolality: the osmolality was measured by freezing point depression osmometer.

Statistical analysis

Normally distributed continuous variables were expressed as mean (standard deviation) and the continuous variables with skewed distribution were expressed as median (range). Student’s t-test or Mann-Whitney test were applied to compare continuous variables as appropriate or ANOVA test (for more than two group comparison). Chi-square or Fishers test was used for discrete variables, as appropriate univariate and multivariate were used to assess the association between duration of hospital stay and other relevant variables. Predictors of in hospital mortality were assessed by Cox-proportional hazard model. To estimate cumulative probability of survival, Kaplan-Meier’s analysis with log rank test was used. A two-sided P value of <0.05 was taken as significant. Data was analysed using IBM SPSS Statistic Software (version 20.0, Chicago, IL, USA) and Medcalc Software (Version 15.11.4, Medcalc Software, Ostend, Belgium).

Management: the possible precipitating factor was removed. If fluid overload was there, fluid restriction was started. Hypertonic saline, normal saline or salt added diet was given as per severity of the patient. More than 1500 mEq of sodium was not administered in a day.

RESULTS

Total 931 patients were screened during the study period. Hyponatremia (Serum sodium <135 mEq/L) was observed in 100 patients (10.7%). There were 73 males (73%) and 27 females (27%). The mean age of patients was 60.1±14.2 with a range of 20 years to 92 years. Above 60 years of age there were 54% of patients while below 40 years of age there were 7% patients (Table 1).

The mean serum osmolality was 272.8±11.38 mosm/kg and urinary osmolality was 359.7±51.6 mosm/kg. The mean serum sodium level was 129.96±1.5mEq/L with a range of 102 mEq/L to 133 mEq/L, the mean urinary sodium was 40.3 mEq/L with a range of 10-75.4 mEq/L. Mild hyponatremia (serum sodium level 130-134

mEq/L), moderate (serum sodium level 120-129 mEq/L and severe hyponatremia (serum sodium level <120 mEq/L) were observed in 73 cases (73%), in 17 cases (17%) and in 10 cases (10%) respectively (Table 2).

Table 1: Age and sex wise distribution of patients.

Age group in years	Male	Female	Total
20-39	7	0	7
40-59	30	9	39
60-79	32	13	45
80-99	4	5	9
Total	73	27	100

Table 2: Type of hyponatremia.

Types	No. of cases	%
Mild hyponatremia	73	73
Moderate hyponatremia	17	17
Severe hyponatremia	10	10
Euvolemia	51	51
Hypovolemia	21	21
Hypervolemic	28	28

Table 3: Clinical features of hyponatremia.

Clinical features	No. of cases	%
CNS symptoms		
Disorientation	20	20
Drowsiness	22	22
Seizure	2	2
Coma	0	0
Non-CNS symptoms		
Fever	28	28
Nausea	24	24
Vomiting	14	14
Hiccup	10	10
Loss of appetite	15	15
Pain abdomen	8	8
Jaundice	4	4
Bilateral leg swelling	9	9

Table 4: Aetiology of hyponatremia.

Aetiology	No. of cases	%
SIADH	34	34
Sepsis	13	13
Diuretics	11	11
Renal	15	15
Endocrine (hypothyroid-8 and hypopituitary-3)	11	11
CVS	6	6
GI loss	5	5
CNS	2	2
CLD	3	3
Pancreatitis	2	2

The incidence of euvolemia, hypovolemia and hypervolemia were 51%, 21% and 28% respectively (Table 2). Euvolemia comprised 36% of mild hyponatremia, 11% moderate and 4% severe hyponatremia while they were 20%, 5% and 3% in hypervolemia and 17%, 1% and 3% in hypovolemia. Acute hyponatremia (<48 hours) was observed in 28% and chronic in 72% patients.

The common comorbidities were hypertension (66%), diabetes mellitus (41%), acute and chronic kidney disease (21%), endocrinopathy (13%), cardiovascular causes (6%), chronic liver disease (3%) and CNS causes (15%). The common CNS symptoms were disorientation (20%), drowsiness (22%), seizure (2%). No one was in coma. The non-CNS symptoms were fever (28%), nausea (24%), loss of appetite (15%), vomiting (14%), hiccup (10%), jaundice (4%), pain abdomen (8%) and bilateral leg swelling (9%) (Table 3).

Analysis of the causes of hyponatremia in this study revealed SIADH, sepsis, chronic liver disease (CLD), pancreatitis, endocrine causes, CVS, renal, diuretics, GI loss and CNS in 34%, 13%, 3%, 2%, 11%, 6%, 15%, 11%, 5% and 2% respectively (Table 4).

The mortality was 7% (7 cases), out of which 4 were males and 3 were females. The mortality was 57.1% after the age of 60 years. In severe hyponatremia it was 3 while 2 each in moderate and severe hyponatremia (P value of 0.005). Mortality was 30% in patients with severe hyponatremia 30% while it was 11.8% in moderate hyponatremia and 2.7% in mild hyponatremia during hospital stay. The probability of survival during hospital stay was higher for patients with mild hyponatremic as compared to patients with moderate or severe hyponatremia (P = 0.004). Out of 7 deaths 4 were in hypervolemic and 3 were in hypovolemia.

Table 5: Difference in baseline demographic, clinical and laboratory parameters of patients with different severity of hyponatremia.

Parameter	Mild hyponatremia	Moderate hyponatremia	Severe hyponatremia	P-value
Age in years mean (\pm SD)	59.7 (14.5)	62.3 (11.9)	63.7 (18.9)	0.492
Male	54 (74.0%)	13 (76.5%)	6 (60.0%)	0.608
Drowsiness	10 (13.7%)	6 (35.3%)	5 (50.0%)	0.009*‡
Disorientation	9 (12.3%)	5 (29.4%)	6 (60%)	0.001‡
Seizure	1 (1.4%)	0 (0.0%)	1 (10.0%)	0.153
Hiccup	6 (8.2%)	3 (17.6%)	1 (10.0%)	0.506
Nausea	13 (17.8%)	5 (29.4%)	5 (50%)	0.060
Vomiting	7 (9.6%)	3 (17.6%)	4 (40%)	0.030‡
Fever	23 (31.5%)	2 (11.8%)	3 (30%)	0.261
Hypertension	14 (19.2%)	6 (35.3%)	4 (40%)	0.172
Diabetes mellitus	11 (15.1%)	4 (23.5%)	4 (40%)	0.148
Hypothyroidism	5 (6.8%)	1 (5.9%)	2 (20%)	0.334
Diuretic use	25 (34.2%)	7 (41.2%)	5 (50.0%)	0.580
Serum osmolarity	276.78 (8.8)	267.67 (4.9)	253.04 (12.3)	0.238
Urine sodium	39.7 (33.0)	36.6 (16.7)	50.75 (28.4)	0.351
Urine osmolarity	363.7 (52.7)	345.7 (53.4)	354.8 (39.3)	0.465
Hospital stay	7.0 (5.0-9.0)	9.0 (6.0-13.5)	12.0 (9.3-14.8)	<0.001*‡

*Significant between mild and moderate hyponatremia, † Significant between moderate and severe hyponatremia, ‡ Significant between Mild and severe hyponatremia.

The duration of hospital stay was 6-14.8 days in 56% patients while it was more than 10 days in 24% and <6 days in 20% patients. On univariate analysis, presence of hypertension and low serum sodium were associated with longer duration of hospital stay. On multivariate analysis low serum sodium at admission was found out to be independently associated with longer duration of hospital stay (P <0.0010). The duration of hospital stay in mild, moderate and severe hyponatremia were 7 days (5-9 days), 9 days (6-13.5 days) and 12 days (9.3-14.8 days) respectively (Table 5).

DISCUSSION

The mean age was 60.5 years with a range of 20 years to 92 years. Above 60 years of age, there were 54% patients while below 40 years of age it was 7%. Hence, incidence of hyponatremia increases with age.^{21,22} In this study, 73% were males and 27% were females. Similar male dominance was reported in earlier studies.²³⁻²⁵ Whereas, few literatures show higher incidence of hyponatremia in females than males.^{26,27} The incidence of hyponatremia was 10.7% in this study. The incidence of hyponatremia

ranges from 1.40%, 22%, and 28.25% in different studies.^{4,5,23}

Prevalence of severe, moderate and mild hyponatremia in this study was 10%, 17% and 73% respectively. The incidence of severe hyponatremia reported in different studies was 2-3%, 28%, 16.4% and 9%.^{4,6,23,28,25} In the present study, the incidence of euvoletic, hypovolemic and hypervolemic hyponatremia was 51%, 21% and 28% respectively which was one with few earlier studies.^{21,28,29}

The commonest CNS symptoms were disorientation (20%), drowsiness (22%), seizure (2%) and coma (0%). Confusion followed by altered sensorium were major symptoms in severe hyponatremia while in another study altered sensorium followed by seizure were the major symptoms.^{23,24} Maqbool M et al, observed confusion in 48%, lethargy in 20% and seizure in 10%.²¹ Agrawal SM et al, observed confusion in 41.4%, altered sensorium in 17.1% and seizure in 29%. None of the patients in this study had coma which is one with an earlier study.²⁴ The non-CNS symptoms were fever (28%), nausea (24%), vomiting (14%), hiccup (10%), loss of appetite (15%), bilateral leg swelling (9%). Nausea was observed in 30% patients by Agrawal SM et al, while it was 12% in another study.^{23,24} Fever was reported in 15.5% in a study.²³

The causes of hyponatremia were SIADH (34%), sepsis (13%), chronic liver disease (3%), pancreatitis (2%), endocrine (11%), CVS (6%), renal (15%), diuretic (11%), GI loss (5%) and CNS (2%). The predisposing factors in the study of Maqbool M et al, were diuretics (34%), SIADH (29%), strokes (15%), and SSRI use (6.5%).²¹ Multiple predisposing factors for development of hyponatremia were reported by many earlier workers.^{23,24}

The mortality rate was 7% (7 cases) in the present study. Out of the 7 cases, 4 were males and 3 were females. Mortality was 57% after the age of 60 years. The mortality was 3 in severe hyponatremia while it was 2 each in mild and moderate hyponatremia, the differences in mortality of patients with different severity of hyponatremia had a 'P' value of 0.005. Mortality during hospital stay was higher in patients in severe hyponatremic group (30%) as compared to mild hyponatremia (2.7%) and moderate hyponatremia (11.8%). The probability of survival during hospital stay was higher for patients with mild hyponatremia as compared to patients with moderate or severe hyponatremia (P =0.004). Out of 7 deaths 4 were in hypervolemia and 3 in hypovolemic. The mortality ranges from 5% to 55% in acute symptomatic patients.¹⁹ The mortality rate was 12% (total 12 patients, out of which 8 males and 4 females) and 13%.^{21,23} No mortality was reported by Agrawal SM et al.²⁴ Maqbool M et al, reported 12 deaths out of which 8 were in hypervolemic and 4 in hypovolemic.²¹ The duration of hospital stay was 6-10 days in 56%, more than 10 days in 24% and <6 days in 20%. On univariate analysis, presence of hypertension

and low serum sodium were associated with longer duration of hospital stay while on multivariate analysis low serum sodium level at admission was found to be associated independently with longer duration of hospital stay (P<0.001). The duration of hospital stay in mild, moderate and severe hyponatremia were 7 days (5-9 days), 9 days (6-13.5 days) and 12 days (9.3-14.8) days respectively. The time taken for recovery varies inversely with the severity of hyponatremia.²⁴ The duration of hospital stay also depends on starting treatment. Delay in starting treatment leads to longer hospital stay.²⁴

CONCLUSION

Occurrence of hyponatremia is common in hospitalized patients. The clinician should be aware of it as early in diagnosis and prompt in management will reduce the mortality as well as duration of hospital stay. The aetiology of hyponatremia should be evaluated and treated. The mortality of hyponatremia depends on the underlying diseases. Hyponatremia of any degree is associated with poor outcome. Proper management of hyponatremia irrespective of aetiology had a better prognosis. Mortality has observed in hypervolemia and hypovolemia in this study. Proper handling of volume status may raise the survival rate.

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