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The Correlation of Hyponatremia with Neurological Features in Adult Patients Admitted in an ICU Setting in a Tertiary Care Centre

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Abstract

Background: Hyponatremia is the most prevalent electrolyte abnormality worldwide, presenting at even higher rates in the ICU setting. It is one of the leading causes of metabolic encephalopathy and can present with a myriad of neurological features. It is defined by a serum sodium level <135 mEq/L. The present study is designed to evaluate the neurological symptoms in a patient with hyponatremia and to correlate them with the degree of hyponatremia. **Aims and Objectives:** 1) To study the neurological manifestations in ICU patients found to have hyponatremia 2) To study the correlation between neurological manifestations and serum sodium level. **Materials and Methods:** This is Prospective Observational study of 2 years duration in which 90 patients were studied with the following criteria: Age ≥18 years, either sex admitted in the ICU having sodium Level of < 135 mMol/L on admission. A thorough neurological examination including Mini Mental Status Examination (MMSE) and Glasgow Coma Scale (GCS) was done at presentation. The data was then analyzed. **Results**: There was a male predominance (64.44%) amongst the study population. Most patients belonged to the age group of 51-60 years (73.3%) followed by > 60 years (31.1%). Disorientation (41.11%) was the most common neurological features followed by drowsiness (31.11%).Maximum number (48.7%) of patients having mild hyponatremia were asymptomatic. At presentation, most had a normal Mini Mental Status Examination (MMSE) score (28.89%) followed by moderate cognitive impairment (27.78%), GCS scores ≥13 was seen in 56.67% population followed by GCS 9-12 (41.11 %). 2 (2.2%) patients succumbed in the study population. **Conclusion:** Hyponatremia is a common electrolyte abnormality causing significant morbidity and mortality, especially in the older age group. It is one of the leading causes of metabolic encephalopathy. As it can be asymptomatic in the initial stages, and is treatable, it should evaluated in all patients with subtle as well as overt neurological signs to prevent further neurological deterioration. MMSE scoring is a useful tool for neurological assessment in hyponatremia.

Keywords: Hyponatremia, Neurological Features, GCS, MMSE

1. Introduction

Hyponatremia is defined as serum sodium level <135 mEq/L. It is the most common electrolyte abnormality seen amongst hospitalized patient's worldwide[1]. Prevalence of hyponatremia in hospital admissions varies between 3.4% to 39.4%[2,3]. While in the ICU setting, it is found to be as high as 34.3%[4].

Hyponatremia presents with a wide variety of symptoms ranging from nausea and malaise, with mild reduction in the serum sodium (Na), to lethargy, decreased level of consciousness, headache, seizures and

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coma. Acute hyponatremia (developing in < 48 hours) can present with severe symptoms of hyponatremic encephalopathy and can culminate into brain herniation and death if not intervened immediately[5].

Assessment of the volume status is helpful in determining the type of hyponatremia as it occurs because of a relatively greater amount of total body water as compared with total body solute[6]. Hypovolemic hyponatremia is associated with clinical symptoms and signs of volume depletion. Hyponatremia without signs of volume depletion or overload is classified as euvolemic. Patients with clinically detected increased Extracellular Fluid (ECF) volume are classified as hypervolemic hyponatremia[7]. It is important to rule out pseudohyponatremia secondary to hyperglycemia and hyperlipidemia. The commonest cause of euvolemic hyponatremia found among different studies is the Syndrome of Inappropriate Antidiuretic Hormone (SIADH)[1,4], however many studies have also found diuretic therapy, congestive cardiac failure and liver disease to be common causes[8].

Urine sodium, serum and urine electrolytes are important basic investigations needed to arrive at the etiology of hyponatremia.

Treatment approach to hyponatremia depends on the type of hyponatremia. Patients with hypovolemic hyponatremia are mainly treated by repleting the ECF volume with Normal Saline (NS). Water restriction and 3% saline is the mainstay of treatment of euvolemic and hypervolemic hyponatremia.

Chronic hyponatremia is to be treated at slower rates, as neurological sequelae are associated with more rapid rates of correction[9,10].

Patients with euvolemic hyponatremia due to SIADH, hypothyroidism, or secondary adrenal failure will respond to successful treatment of the underlying cause, with an increase in plasma Na concentration.

However, not all causes of SIADH are immediately reversible, necessitating pharmacologic therapy to increase the plasma Na concentration. Finally, there are patients with hyponatremia due to beer potomania and low solute normal diet.

The current study will correlate neurological manifestations of hyponatremia with the levels of hyponatremia and asses the improvement on correction of hyponatremia.

2. Aims and Objectives

- To study the neurological manifestations seen in patients of Hyponatremia (Sodium Level <135 mEq/L) admitted in ICU.
- To study the demographic demographic profile of these patients.
- To study the correlation between neurological manifestations and serum sodium level in these patients.

3. Materials and Methods

- **Study Design:** Prospective Observational Study
- **Study Setting:** Intensive Care Unit of a Tertiary Care Centre and Teaching Hospital.
- **Duration of Study**: August 2016 To September 2018
- **Study Population :** 90 patients fitting in the inclusion and exclusion criteria were studied
- Sample Size Calculation Formula:

$Z^2 p^* q L^2$

Where Z = 1.96 (critical value)

p = proportion of the diseased P = 0.06

q = 1-p

L = margin of error = 5%

3.1 Eligibility Criteria

3.1.1 Inclusion Criteria

Adult patients of either sex (age 18 yrs or more) admitted in the ICU for a non-neurological illness having sodium level of < 135 mmol/l on admission or during first 48 hours

3.1.2 Exclusion Criteria

- Primary disease involving the central nervous system.
- Patients under the influence of a CNS depressant drug such as alcohol, barbiturates, phenytoin, phenothiazines, benzodiazepines, methanol, ethylene glycol, paraldehyde.
- Presence of hypoxemia grossly assessed by pulse oximeter saturation <90%.

- Presence of hypoglycemia (blood glucose <70mg/dl).
- Patients with eGFR<60 ml/min/1.73 m^2 as determined by MDRD Study Equation.
- Patients with Minimal Hepatic Encephalopathy or Overt Hepatic encephalopathy as determined by clinical features and administering rapid inhibitory control test for MHE (neuropsychological testing) i.e. Number connection test.
- Patient who has not given written informed consent.

4. Methodology

In this study, hyponatremia was defined as a level of serum sodium less than 135 mmol/l i.e. ≤ 134 mmol/l.[28]

Those patients fulfilling the inclusion and exclusion criteria were included in the study. Patients were considered after correction of the exclusion criteria, for example, after the correction of hypoglycemia. Only the patients giving valid informed consent were considered. Institutional ethical clearance was taken.

Adult patients 18 years and more admitted in the ICU of a Tertiary Care Centre, and not suffering from any disease primarily involving the central nervous system were included in this study.

Serum Sodium Levels of all patients admitted to ICU were estimated at the time of admission. The patients were subjected to detailed history taking and clinical neurological examination at presentation.

The findings were then correlated with serum sodium levels.

The observed GCS, MMSE and clinical features including examination findings were compiled into those appearing at levels <120 mEq/L (severe hyponatremia), 120-129 mEq/L (moderate hyponatremia) and <130m Eq/L-134mEq/L (mild hyponatremia)[18,19]. Symptoms studied were headache, restlessness, weakness, disorientation, drowsiness, tremors, hallucinations, seizures, psychosis, hemiparesis/hemiplegia, coma.

Demographic distribution, seasonal variations were also analyzed.

4.1 Statistical Analysis

All the collected data was entered in Microsoft Excel sheet and then transferred to SPSS software ver.17 for analysis. Qualitative data was presented as frequency and percentages and analysed using chi-square test. P-value < 0.05 was taken as level of significance.

5. Observation and Results

There was a male predominance (64.44%) amongst the study population as compared to females (35.56%). Most of the study population belonged to the age group

Table 1. Age and sex distribution in the study population

Age	Total	Male	Female
18-30 years	5 (5.6%)	3 (5.2%)	2 (9.4%)
31-40 years	6 (6.7%)	4 (6.9%)	2 (12.5%)
41-50 years	15 (16.7%)	11 (19%)	4 (34.4%)
51-60 years	36 (40%)	23 (39.7%)	13 (71.9%)
>60 years	28 (31.1%)	17 (29.3%)	11 (53.1%)
Total	90(100%)	58 (100%)	32(100%)

of 51-60 years (40%) followed by > 60 years (31.1%) and 41-50 years (16.7 %) (Table 1).

As seen in the table 2, disorientation (41.11%) was the most common neurological feature observed amongst the study population followed by drowsiness (31.11%), seizures (21.11%), weakness/hemiparesis (20%) and restlessness (5.56%). 24.44% patients were asymptomatic. In age group of 18-30 years, most patients (80%) were asymptomatic. Disorientation (20%) and headache (20%) were commonest neurological features; in age group of 31-40 years, 33.3% patients were asymptomatic while the rest had Muscle cramps, Restlessness, Hemiplegia/ Hemiparesis, Drowsiness and Tremors (16.7% each). In the age group of 41-50 years, Disorientation (40%) was the commonest clinical presentation. In the age group of 51-60 years, Drowsiness (27.8%), and Disorientation (25%) were the commonest neurological features. Patients more than 60 years presented with Disorientation (60.7%) and Drowsiness (50%).

It is inferred that the percentage of asymptomatic patients decreased as the age group increased.

Table 2. Comparison of different age group with various neurological features amongst study population

Age group	18-30 years	31-40 years	41-50 years	51-60 years	>60 years	Total (% out of total)
Headache	1 (20%)	0 (0%)	0 (0%)	3 (8.33%)	6(21.42%)	10(11.1%)
Muscle cramps	0 (0%)	1 (16.7%)	1 (6.7%)	1 (2.8%)	2 (7.1%)	5(5.7%)
Restlessness	0 (0%)	1 (16.7%)	3 (20%)	3 (8.33%)	5 (17.9%)	12(13.3%)
Hemiplegia/ Hemiparesis	0 (0%)	1 (16.7%)	5 (33.3%)	5 (13.9%)	7 (25%)	18(20%)
Tremors	0 (0%)	1 (16.7%)	1 (6.7%)	0 (0%)	1 (3.6%)	3(3.3%)
Seizures	0 (0%)	1 (16.7%)	3 (20%)	5 (13.9%)	7 (25%)	19(21.1%)
Disorientation	1 (20%)	3 (8.33%)	6 (40%)	9 (25%)	17 (60.7%)	37(41.1%)
Hallucinations	0 (0%)	0 (0%)	0 (0%)	2 (5.6%)	3 (10.7%)	5(5.7%)
Drowsiness	0 (0%)	1 (16.7%)	3 (20%)	10 (27.8%)	14 (50%)	28(31.1%)
Coma	0 (0%)	0 (0%)	0 (0%)	1 (2.8%)	1 (3.6%)	2(2.2%)
Asymptomatic	4 (80%)	2 (33.3%)	6 (40%)	5 (13.9%)	2 (7.1%)	22(24.4%)
No. of pts in age group	5(100%)	6(100%)	15(100%)	36(100%)	28(100%)	90(100%)

Also, mild hyponatremia and moderate hyponatremia was observed most commonly in the age group of 51-60 years (46.15% and 36.36%) and severe hyponatremia was observed most commonly in the age group of > 60 years (61.1%) (Table 2).

Maximum number (48.7%) of patients having mild hyponatremia were asymptomatic on presentation. Otherwise, Disorientation (17.9%) was the most common presenting feature in them, followed by Headache (10.3%). Patients with moderate hyponatremia presented with Disorientation (30.3%) followed by Drowsiness (24.2%). Most of the patients in the severe hyponatremia group had Disorientation (94.4%) and Drowsiness (94.4%). This was the only group in which patients went into coma (11.11%).

The percentage of asymptomatic patients decreased and severity of symptoms increased as the degree of hyponatremia increased. (Table 3).

Table 3. Comparison of different neurological features with grades of hyponatremia amongst study population

Clinical feature	Mild hyponatremia 130-134mEq/L	Moderate hyponatremia 120-129 mEq/L	Severe hyponatremia <120 mEq/L	Total
Headache	4 (10.3%)	4 (12.1%)	2 (11.1%)	10 (11.1%)
Muscle Cramps	0 (0%)	1 (3%)	4(22.2%)	5 (5.6%)
Restlessness	1(2.6%)	6 (18.2%)	5 (27.8%)	12(13.3%)
Hemiplegia/hemiparesis	0 (0%)	7(21.2%)	11(61.1%)	18(20%)
Tremors	0 (0%)	1 (3%)	2(11.1%)	3(3.3%)
Seizures	0 (0%)	4 (12.1%)	12 (66.7%)	16(17.8%)
Disorientation	7 (17.9%)	10 (30.3%)	17 (94.4%)	36(40%)
Hallucinations	0 (0%)	2 (6.1%)	3 (16.7%)	5(5.6%)
Drowsiness	1 (2.6%)	8 (24.2%)	17 (94.4%)	28(31.1%)
Coma	0 (0%)	0 (0%)	2 (11.1%)	2(2.2%)
Asymptomatic	19 (48.7%)	3 (9.1%)	0 (0%)	22(24.4%)
Total no. of pts	39(100%)	33(100%)	18(100%)	

Table 4. Mini Mental Status Examination (MMSE) Score with grades of hyponatremia amongst study population on presentation

Mini Mental Status Examination Score on presentation	Mild hyponatremia 130-134mEq/L	Moderate hyponatremia 120-129 mEq/L	Severe hyponatremia <120 mEq/L	Total
Normal (≥25)	25 (64.1%)	1 (3.03%)	0 (0%)	26 (28.89%)
Mild impairment (20-24)	12 (30.77%)	4 (12.12%)	3 (16.67%)	19(21.11%)
Moderate impairment (13-19)	2 (5.13%)	18 (54.55%)	5 (27.78%)	25 (27.78%)
Severe impairment (<12)	0 (0%)	10 (30.30%)	10 (55.56%)	20 (22.22%)
	39 (100%)	33 (100%)	18 (100%)	90 (100%)

Chi square test, P value-0.0001

Table 5. Glasgow Coma Scale (GCS) Score with grades of hyponatremia amongst study population at presentation

GCS at presentation	**Mild hyponatremia 130-134mEq/L**	**Moderate hyponatremia 120-129 mEq/L**	**Severe hyponatremia <120 mEq/L**
Mild (13-15)	36 (92.31%)	11 (33.33%)	3 (16.67%)
Moderate (9-12)	3 (7.69%)	21 (63.64%)	13 (72.22%)
Severe (≤8)	0 (0%)	1 (3.03%)	2 (11.11%)
Total	39 (100%)	33(100%)	18 (100%)

Chi square test, P value-0.0001

Most of the study population had a Normal MMSE score (28.89%) followed by Moderate (27.78%) and Severe (22.22 %) impairment.

Most of the patients with mild hyponatremia, had a Normal Mini Mental Status Examination score (64.1%) on presentation. With moderate hyponatremia, most of the study population had moderate impairment of MMSE score (54.55%) followed by severe impairment (30.30%). Patients with severe hyponatremia had mostly severe impairment of MMSE score (55.56%) followed by moderate impairment (27.78%) and the difference was statistically significant. (Table 4).

As the degree of hyponatremia worsened, the MMSE score worsened.

Most of the patients with mild hyponatremia, had a GCS score ≥13 (92.31 %) at presentation. None of the patients had a GCS score ≤8. With moderate hyponatremia, most of the study population (63.64%) had GCS score 9-12 followed by normal GCS in 33.33%. Amongst those with severe hyponatremia, most (72.22%) had a GCS score 9-12and the difference was statistically significant (Table 5).

As the degree of hyponatremia worsened, the GCS worsened.

Mortality was observed in 2.2% (2 cases) of study population; and only in the severely hyponatremic group.

5. Discussion

Hyponatremia is defined as a serum sodium level <135 mEq/l.[11] It is the most common electrolyte disorder among hospitalized patients[12,13]. It is associated with mortality and morbidity ranging from 5-50% depending on severity and acuity of onset[14].

In this study, patients have been categorized into mild (130-134mEq/L, moderate (120-129 mEq/L) and severe hyponatremia (<120 mEq/L).

5.1 Demographic Profile

In the present study, there was a male predominance (64.44%) amongst the study population as compared to females (35.56%). Similarly, in a study by Prakash Babaliche *et al.,* out of 100 patients admitted with moderate-to-severe hyponatremia, slight male preponderance was observed[15]. A gender distribution pattern similar to the current study was also reported by Rahil *et al.* wherein 62.3% patients with hyponatremia were males and 37.7% were females[16]. On the contrary, some studies have higher incidence of hyponatremia in females as compared to males[17,18], such as the study done by Ashraf *et al.,* showing a female predominance (71%)[19].

Most of the current study population belongs to the age group of 51-60 years (73.3%) followed by > 60 years (31.1%) and 41-50 years (16.7 %).

This finding is in agreement with the study conducted by Paniker G.I *et al.,* in which the patients in the study population predominantly belonged to the age groups 51-60 yrs (23%) and 61-70 yrs (23%)[20].

5.2 Neurological Features

In this study, Disorientation (41.11%) was the most common neurological feature observed amongst the study population followed by Drowsiness (31.11%), Seizures (21.11%), hemiplegia/hemiparesis (20%), Restlessness (13.33%), Headache (11.11%) and Muscle cramps and hallucinations (5.56%) each. In the age group of 18-30 years, Disorientation and headache were the commonest features (20% and 20%); in the age group of 31-40 years, Muscle cramps, Restlessness, Hemiparesis/hemiplegia, Drowsiness and Tremors were seen the most (16.7% each); in the age group of 41-50 years, Disorientation and hemiplegia/ Hemiparesis were the commonest neurological features (40% and 33.3%); in the age group of 51-60 years, Drowsiness, and Disorientation were seen most commonly (27.8% and 25%); in age group of more than 60 years, Disorientation and Drowsiness were the most frequent (60.7% and 50%).

These findings are in agreement with the study conducted by Paniker G.I *et al.,* in which 34% patients had presented with confusion which was highest among all the variables followed by seizures and coma[20].

Disorientation was seen in 41.11% of patients which is much lesser than that reported by Ellis *et al.,* in his study where 76% of the patients had clouding of consciousness. Ellis *et al.,* in their study also reported that 11% patients had coma which was similar to both studies[21].

Overt neurological symptoms most often are due to very low serum sodium levels usually <115 mEq/L, resulting in intracerebral osmotic fluid shifts, and brain edema. In the present study, the percentage of asymptomatic patients decreased and severity of symptoms increased as the degree of hyponatremia increased. Similarly in the study conducted by Shanmugasundaram Rajamani *et al.,*[22] neurological symptoms were reported amongst patients with severe hyponatremia rather than mild and moderate grade of hyponatremia and this is similar to the work done by Clayton *et al.,* and Nzerue et al[8,23].

5.3 Mild, Moderate and Severe Hyponatremia

In the current study, 43.33% patients had mild hyponatremia (130-134mEq/L), 36.67% patients had moderate hyponatremia (120-129 mEq/L) and 20% had

severe hyponatremia (<120 mEq/L). A study conducted by Chowdhury *et al.* among 70 patients, reported mild hyponatremia, moderate hyponatremia, and severe hyponatremia in 27.14%, 37.14%, and 35.72% of the patients, respectively[24].

5.4 Hyponatremia vs Age Group

In the present study, Mild hyponatremia was observed most commonly in the age group of 51-60 years (46.15%) followed by 41-50 years (20.51%), Moderate hyponatremia was observed most commonly in the age group of 51-60 years (36.36%) followed by >60 years (36.36%) and severe hyponatremia was observed most commonly in the age group of > 60 years (61.1%) followed by 51-60 years (33.3%). The incidence of hyponatremia is higher in the elderly, owing to the impaired water and electrolyte homeostasis due to dietary and environmental variations[25]. In accordance with other reports[26,27] in our study, hyponatremia was more prevalent among the elderly patients than in the younger patients.

5.5 Degree of Hyponatremia *vs.* Neurological Features

Maximum number (48.7%) of patients having mild hyponatremia were asymptomatic. Otherwise, Disorientation (17.9%) was the most commonly observed neurological feature in Mild hyponatremia followed by Headache (10.3%); Disorientation (30.3%) was the most commonly observed clinical feature observed in moderate hyponatremia followed by Drowsiness (24.2%). In severe hyponatremia, Disorientation (94.4%) and Drowsiness (94.4%) were the most frequently observed features followed by Seizures (66.7%). This was the only group in which patients went into coma (11.11%).

A study by Rahil *et al.* showed CNS involvement in 24.5% of the patients with symptoms that ranged from Disorientation to coma[16]. Similarly, Prakash Babaliche *et al.,* reported majority of the patients had altered sensorium, which was more common with severe hyponatremia than moderate hyponatremia[15].

5.6 Mini Mental Status Examination (MMSE) Score

In the present study, most of the study population had a Normal Mini Mental Status Examination score (28.89%) followed by moderate cognitive impairment (27.78%) and Severe cognitive impairment (22.22%).

Patients with mild hyponatremia had maximum percentage of patients with a Normal MMSE score (64.1%) followed by mild cognitive impairment (30.77%) and moderate (5.13%) impairment; in patients with moderate hyponatremia, most of the study population had moderate impairment of MMSE (54.55%) followed by severe impairment (30.30%); in patients with severe hyponatremia, most of them had severe cognitive impairment as per MMSE score (55.56%) followed by moderate impairment (27.78%). As the degree of hyponatremia worsened, the MMSE score worsened and the difference was statistically significant.

5.7 Glasgow Coma Scale (GCS) Score

In the present study, most of the study population had a GCS score ≥ 13 (56.67%) followed by GCS score 9-12 (41.11 %) and GCS score ≤8 (2.22%). A study by Pillai et al showed GCS ≤ 10 in 36% patients[28].

Of the patients with mild hyponatremia, most had a GCS score ≥ 13 (92.31 %) followed by a GCS score 9-12 (7.69 %); In patients with moderate hyponatremia, most of the study population had a GCS score 9-12 (63.64%) followed by GCS score ≥ 13 (33.33%); in patients with severe hyponatremia, 72.22% had a GCS score 9-12, 16.67% had a GCS score ≥ 13, followed by 11.11% having GCS score ≤8.

As the degree of hyponatremia worsened, the GCS worsened and the difference was statistically significant.

5.8 Mortality

In the present study, mortality was observed in 2.2% (2 cases) of study population. This finding is in agreement with the study conducted by Paniker G.I *et al.,* in which out of 100 patients there were 7 deaths, all which occurred in patients with severe hyponatremia[20]. Similarly in the study conducted by Shanmugasundaram Rajamani, *et al.,* mortality was reported only in 5 patients (2.1%) with severe hyponatremia[22].

6. Conclusion

Disorientation, Drowsiness, Seizures and Hemiplegia/ hemiparesis were the most common neurological

manifestations observed in this study. The new onset of such symptoms must herald the search for hyponatremia as one of the causes of neurological impairment.

The severity of neurological manifestations increases as the degree of hyponatremia advances. This is reflected in the manifesting symptoms as well as the cognitive decline measured by the Mini Mental Scale Examination and also the level of consciousness as measured by the Glasgow Coma Scale. More studies are however required, using MMSE and GCS for clinical assessment.

Hyponatremia is a common electrolyte abnormality causing significant morbidity and mortality, especially in the older age group. As it can be asymptomatic, and is treatable, it should be measured in all patients at risk on a regular basis to prevent sudden neurological decompensation.

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