



HYPONATREMIA – ETIOLOGY AND CLINICAL PRESENTATION IN A TERTIARY CARE CENTER

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KEYWORDS :

INTRODUCTION

Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is frequently encountered in the intensive care setting. Treatment varies significantly according to the timing of onset and etiology of the disorder. Inadequate or improper treatment may lead to brain edema or demyelination with life-threatening consequences. Hyponatremia, or low blood sodium, is frequently defined as serum sodium concentration < 135 mEq/L, and it represents a relative excess of total body water to sodium.^{1,2}

Hyponatremia is common in hospitalized patients, occurring in 30% to 40% of patients with a serum sodium of < 135 mEq/L.³ DeVita et al found that approximately 25% to 30% of patients admitted to an intensive care unit (ICU) had hyponatremia defined as serum sodium < 134 mEq/L.⁴

The clinical presentation has a wide spectrum and varies from patient to patient, from being asymptomatic, to ones having seizures and coma. Most of the patients with hyponatremia have either non-specific symptoms or symptoms due to underlying system involved. Although majority of cases are mild and asymptomatic, hyponatremia is important clinically because Acute severe hyponatremia can cause substantial morbidity and mortality. The aim of this study is to evaluate the clinical features and etiology of hyponatremia in patients admitted a tertiary care hospital.

MATERIALS AND METHODS

The present 1-year cross-sectional observational study included 100 adult patients with moderate-to-severe hyponatremia admitted under the Department of Medicine from October 2012 to April 2014. Patients aged ≥ 18 years with moderate-to-severe hyponatremia (≤ 125 mmol/L) admitted to the MICU were included in the study. The exclusion criteria comprised of cases with hyperglycemia, hyperlipidemia, and proteinemia. Ethical clearance was obtained from the Institutional Ethical Committee and after explaining the purpose of the study. Written consent from all the participants was obtained before data collection.

INSTRUMENTATION

Demographic data, including age and sex, were obtained from the patients. A history of other comorbid conditions along with presenting complaints was noted. Further, these patients were subjected to a physical examination for evaluating the clinical signs. The patients underwent the investigations

including, complete blood count, random blood sugar, liver function tests, renal function tests, serum osmolality, urine osmolality, serum sodium, and urine sodium. Based on the investigations, the type of hyponatremia was determined as euvolemic hyposmolar, hypervolemia hyposmolar, and hypovolemic hyposmolar. Following this categorization, the etiology was determined and evaluated in different types of hyponatremia. All data thus obtained was entered in a structured Proforma.

RESULTS

A total of 100 patients were studied who were admitted with hyponatremia to hospitals under Kasturba Medical College, Mangalore between October 2012 and April 2014. The maximum numbers of patients were in the age group of 61-70(28%). There were more males than females in the study.

The total of 30% was asymptomatic with documented hyponatremia. The lowest serum sodium amongst asymptomatic patients was 109. Among those who were symptomatic (symptoms pertaining to hyponatremia) most of them had a combination of symptoms. About 40% had lethargy, 19% had disorientation, 19% had vomiting, 12% had anorexia, 5% patients had seizure, 2% patients had coma, 1% patients had hiccups.

Hypotonic hyponatremia was seen in 68 patients, 17 patients had isotonic hyponatremia, 15 patients had hypertonic hyponatremia.

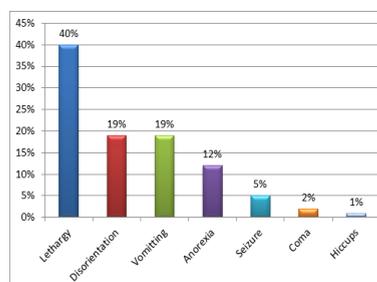


Fig.1: Symptoms at presentation

Pre-existing illness: In our study, 14 patients had Hypertension, 12 patients had Diabetes Mellitus, 6 patients had Chronic kidney disease. Ten patients had history of Tuberculosis, 11 patients had Retroviral disease.

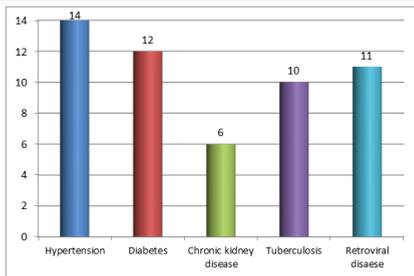


Fig.2: Pre-existing illness

Systems involved at presentation:

A total of 23 patients had pulmonary disorder, 14 patients had gasterointestinal disorder, 13 patients had neurological disease, 12 patients had malignancy, 9 patients had renal disorder, 29 patients had other disorders (endocrine, haematological).

Volume status:

Largest proportion of patients was euvolemic (61 patients). Others were hypovolemic (25 patients), hypervolemic (14 patients). Among the 61 patients with euvolemia, 38 patients had SIADH.

Table 1: Laboratory parameters of cases that presented with hyponatremia

| S. no | Laboratory parameter | n | Range | Mean | Standard deviation |
|-------|--|-----|--------------|--------|--------------------|
| 1 | Plasma glucose (mg/dl) | 86 | 73 - 522 | 151.12 | 92.96 |
| 2 | Serum urea (mg/dl) | 100 | 7 - 162 | 34.17 | 25.39 |
| 3 | Serum creatinine (mg/dl) | 100 | 0.3 - 7.7 | 1.24 | 1.16 |
| 4 | Serum sodium (mEq/L) | 100 | 100 - 134 | 122.23 | 9.22 |
| 5 | Serum triglyceride (mg/dl) | 75 | 20 - 276 | 104.95 | 55.40 |
| 6 | Serum potassium (mEq/L) | 98 | 1.6 - 6.3 | 4.14 | 0.81 |
| 7 | Serum protein (g/dl) | 64 | 4 - 9.5 | 6.74 | 0.97 |
| 8 | Serum uric acid (mg/dl) | 92 | 0.9 - 10.60 | 3.70 | 1.84 |
| 9 | Serum osmolality mOsmol/kg serum water) | 100 | 199 - 350 | 264.68 | 25.28 |
| 10 | Serum TSH (mIU/L) | 92 | 0.10 - 14.79 | 2.10 | 1.88 |
| 11 | Serum cortisol (mg/dl) | 87 | 1.34 - 338.7 | 33.95 | 38.95 |
| 12 | Spot urine sodium (mEq/L) | 99 | 4 - 215 | 60.50 | 40.82 |
| 13 | Urine osmolality (mOsmol/kg serum water) | 97 | 66 - 892 | 351.84 | 177.16 |

Aetiology of hyponatremia:

Forty four patients fulfilled the criteria for SIADH. Twenty five patients had depletional hyponatremia and twelve patients had dilutional hyponatremia. Six patients had pseudo hyponatremia. Twelve patients had multiple aetiologies causing hyponatremia, amongst these, 4 patients had SIADH plus depletional hyponatremia, other causes being hypopituitarism with hypocortisolism (patient no. 25), hypopituitarism + depletional + SIADH (patient no. 61), hypothyroidism + SIADH (patient no.2, 73), SIADH + drug induce hypocortisol hyponatremia (patient no.84), hypocortisol/drug induced depletional (patient no. 85), depletional with primary hyperaldosteronism (patient no. 91). Pseudohyponatremia + polydipsia (patient no. 32). One patient was undiagnosed.

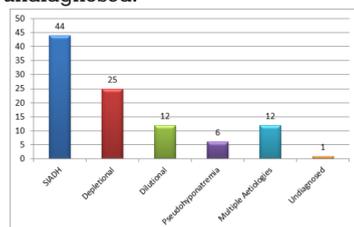


Fig.3: Aetiology of hyponatremia

Aetiology of SIADH: Amongst patients with SIADH, 13 cases were due to malignancy, 8 cases had cerebrovascular accident, 6 had HIV associated condition, 4 had pneumonia, 3 had pulmonary tuberculosis. Cause could not be determined for rest of the cases.

Aetiology of depletional hyponatremia (25 cases): In Fifty percent patients hyponatremia was drug induced, 25% was due to vomiting and rest, due to Pulmonary Tuberculosis, Lower respiratory tract infection, urosepsis, etc. Amongst drug induced depletional hyponatremia (12cases), all the patients were on thiazide diuretics.

Amongst dilutional hyponatremia: Majority (6 cases) were due to decompensated chronic liver disease.

Aetiology in patients with severe hyponatremia (sodium < 120): SIADH (12 patients), depletional (13 patients), dilutional (4 patients), multiple etiological factors causing hyponatremia (9 patients). Amongst the patients with depletional hyponatremia, thiazide diuretics were the cause in 50% patients.

DISCUSSION

Our study was conducted on 100 patients who presented with hyponatremia (serum sodium less than 135 mEq/L). Out of the 100 patients studied there were 61% males and 39% females with a ratio of 1.56:1. The mean age of presentation in our study was 58.8, which was comparable to study by Anderson et al where the mean age was 58.⁵

Incidence of hyponatremia has been shown to have direct correlation with age.⁶ In our study most of the patients were in the age group of 41-80yrs (83%), while maximum number of patients were in the age group of 61-70 yrs (28%). Multiple co morbidities like Hypertension and Diabetes Mellitus are present in this age group where the disease or treatment is likely to predispose a patient to hyponatremia. Use of diuretics is also common among the elderly patients, which has been a major cause of hyponatremia in hospitalized patients. Hawkins et al noted that increasing age, was independently associated with hyponatremia at presentation.⁶ A study done by Chen et al on elderly patients also showed that nutritional status is also a risk factor in developing hyponatremia in elderly.⁷

In our study 70% of the patients had symptoms attributable to hyponatremia at presentation. The rest of the patients (30%) did not have evident clinical manifestations of hyponatremia, but presented with the symptoms of the system involved. Respiratory system was the commonest system involved (23%). Other systems involved were gastrointestinal (14%), renal (9%) and neurological (13%).

The commonest symptom of presentation was lethargy (40%) followed by vomiting (19%). Amongst the other symptoms at presentation were neurological symptoms like disorientation (19%), seizure (5%) and coma (2%). Lethargy was also the commonest symptom in patients with severe hyponatremia (sodium < 120 mEq/L) followed by disorientation (11 patients).

In a study by Nzerue et al on outcome of hyponatremia in hospitalized patients, 52.9% patients had neurological manifestations.⁸ These included seizures, reduced consciousness level, confusion, unsteadiness and falls. In the study we conducted, 31% patients had varied neurological manifestations of hyponatremia. The reason for this difference being, the former study was conducted only on patients with severe hyponatremia. In a study by Aasina yawar et al in Karachi, a quarter of patients presented with neurological manifestations, which was similar to our results.⁹ Major pre-existing illness amongst our patients was hypertension (14%), diabetes mellitus (12%) and retroviral disease (12%).

Hyponatremia can be classified into hypotonic and non hypotonic. Non hypotonic hyponatremia has been further classified into isotonic hyponatremia, hypertonic hyponatremia and pseudo hyponatremia.^{10,11} In our study 68% of the patients had hypotonic hyponatremia, 17% had isotonic hyponatremia, 15% had hypertonic hyponatremia.

All the patients were classified as hypovolemic, euvolemic or hypervolemic depending on the volume status which was determined by clinical evaluation. It was found that 61% of the patients were euvolemic, 25% were hypovolemic and 14% were hypervolemic. This was similar to the other studies, Hochman¹² (50%) and Nandini et al¹³(50.74%), which showed maximum percentage of euvolemic patients.

According to a study done by Berghmans T, SIADH was found to be the most frequent cause of hyponatremia.¹⁴ In our study, 44 patients out of 100 fulfilled the criteria for SIADH which was the leading cause of hyponatremia. Similarly in another Indian study done by MY Rao et al in elderly, commonest cause of hyponatremia was found to be SIADH.¹⁵

A common cause of hyponatremia in patients with cancer is syndrome of inappropriate secretion of antidiuretic hormone (SIADH) which may result from ectopic production of arginine vasopressin (AVP) by tumor tissue. In our study 13 out of 44 patients with SIADH had cancer, commonly head and neck. Other risk factors which increased the possibility of hyponatremia were chemotherapy, vomiting, pain, narcotic drugs and physical and emotional stress.

Other causes of SIADH being cerebrovascular accident (8 cases) and HIV associated conditions (6 cases). Four patients had pneumonia, 4 had pulmonary tuberculosis, while cause could not be determined for rest of the 11 cases.

Depletional hyponatremia (hypovolemic hyponatremia) was detected in 25% of the cases, this being the second most common cause of hyponatremia. A commonest cause of depletional hyponatremia was found to be drug induced (50%). All of the 12 patients with drug induced hyponatremia were on thiazide diuretics. Hyponatremia is a common complication of thiazide diuretics, as seen in studies by Byatt CM and Sunderam SG.^{16,17}

Vomiting is a strong inducer of ADH release. In our study, out of 25 patients of depletional hyponatremia, 5 were due to vomiting. Gastroenteritis was the commonest cause for vomiting (4 patients).

Dilutional hyponatremia was seen in chronic liver disease (6 patients), COPD corpulmonale (2 patients), dilated cardiomyopathy (1 patient), chronic kidney disease (2 patients) and ascites due to ovarian mass (1 patient).

Pseudohyponatremia is a falsely low serum sodium measurement. It occurs in cases of extreme hyperlipidemia or hyperproteinemia when serum sodium is measured by some laboratory methods.¹⁸ In our study 6 patients were diagnosed as pseudohyponatremia, 2 patients had hyperlipidemia, 1 patient had hyperproteinemia and 3 patients had hyperglycemia.

Twelve percent of the patients in our study had multiple etiologies. Previously it has been seen that in varying proportion of patients hyponatremia has been attributed to a multiple etiologies. A couple of studies by Clayton et al¹⁹ and Nzerue et al⁸ had 75% and 10.9% patients with hyponatremia due to multiple etiologies. It is important to determine all the factors causing hyponatremia as the treatment depends on the etiology and thus correct measures could be taken accordingly.

Mean value of sodium in our study was 122.23 mEq/L (100 mEq/L - 134 mEq/L). This was a little lower than mean obtained by study done by Nandini et al.¹³

Plasma glucose level was calculated in 86 patients with range varying from 73-522 mg/dl. It was this high glucose values which was responsible for the presence of pseudohyponatremia in our study. Similar observation holds true for serum triglycerides (range 20-276 mg/dl).

Evaluation of serum osmolality was done in all 100 patients and mean value was determined to be 264.68 mOsmol/kg water which goes well with our observation that most of the cases studied were true hyponatremias (serum osmolality < 280 mOsmol/kg serum water).

The mean value of spot urine sodium was 60.50 mEq/L. This was because of the fact that the common aetiology of hyponatremia was SIADH.

In patients with severe hyponatremia (sodium < 120, n = 38), the commonest aetiology was depletional hyponatremia (13 patients). SIADH was the next common cause (12 patients). This was similar to the study done by Wong R et al²⁰, in which they had obtained similar results.

CONCLUSION

Based on the findings of this study, it may be concluded that hyponatremia can present with varied clinical manifestations. The presentation can vary from mild symptoms such as vomiting, lethargy, and malaise to severe forms such as confusion, seizure, and coma. Majority of patients report CNS symptoms and these patients are likely to have euvolemic hyposmolar hyponatremia with SIADH as the predominant cause. Clinicians need to be aware about the common occurrence of hyponatremia, its early identification, and its association with a large variety of diseases. Therefore, evaluating for the cause of hyponatremia is equally important, as treating the underlying cause would prevent considerable morbidity and mortality associated with this enigmatic electrolyte disorder.

ANNEXURES

ETHICS COMMITTEE APPROVAL



Kasturba Medical College, Mangalore
A constituent college of Manipal University



October 18, 2012

Dr. Taha Perwaiz Sethjiwala
PG in Dept of Medicine
Kasturba Medical College, Mangalore.

Dear Dr. Taha Perwaiz Sethjiwala

Ref: "Characterization of Hyponatremia in Hospitalized Patients"
Sub: Institutional Ethics Committee approval to conduct the above mentioned study

We have received from you the following documents:
1. Research Protocol
2. Informed consent form in English and Kannada

At the Institutional Ethics Committee meeting held on September 28, 2012, the above mentioned documents were examined and discussed. After consideration, the committee has decided to approve the aforementioned study related documents in their presented form.

The members who attended the meeting at which your protocol was discussed are:

- | | |
|--|------------------|
| 1. Dr. M.S.Vidyasagar, Professor & Head Dept of Radiotherapy | Chairperson |
| Father Mullers Medical College, Mangalore | Member |
| 2. Dr. U. Anand Kini, Professor of Surgery | Member |
| 3. Dr. Madhusudan Upadya, Professor of Anaesthesiology | Member |
| 4. Mr. P. Ranjan Rao, LLB Advocate | Member |
| 5. Dr. Goopalakrishna Bhat, Additional Professor of Microbiology | Member |
| 6. Dr. Sheethal Ullal, Associate Professor of Pharmacology | Member |
| 7. Mr. M. Shashidhar Kotian, Statistician | Member |
| 8. Dr. Kundabala M, Associate Dean, MCODS, Mangalore | Member |
| 9. Dr. Satheesha Rao, Professor and Head of Psychiatry | Member |
| 10. Dr. Malini Hebbar, Professor of English | Member |
| 11. Dr. Shalini Shenoy, Professor of Microbiology | Member Secretary |
| 12. Ms. Madhumathi HS, Finance Executive | Member |

It is to be noted that neither you nor any of your proposed study team members was present during the decision making procedure of the Institutional Ethics Committee. You are required to submit a report to the Committee at the completion of the project.

Yours Sincerely

Shalini Shenoy
Dr. Shalini Shenoy
Member Secretary IEC



PROFORMA

1. Patient's name: _____ Date: _____
2. Age:
3. Sex:
4. Date of admission:
5. Symptoms:
 - a) Lethargy / disorientation / muscle cramps / agitation.
 - b) Shortness of breath / orthopnea.
 - c) Fever / cough / haemoptysis.
 - d) Distension of abdomen / hiccups / anorexia / vomiting.
 - e) Weight loss.
 - f) Focal neurological deficit / hoarseness of voice / dysphagia.
 - g) Coma / seizures.
 - h) Excessive water intake.
6. Past history: Similar episode / tuberculosis / renal failure / hypothyroidism / adrenal insufficiency / Steroid intake.
7. Personal history: Menstrual history.
8. Treatment history: Thiazides / Nicotine / Chlorpropamide / Tolbutamide / Clofibrate / Cyclophosphamide / Morphine / Barbiturate / Vincristine / Carbamazepine / Acetaminophen / NSAIDS / Antipsychotics / Antidepressants / Heparin.
9. General examination: Level of consciousness / built / pallor / icterus / cyanosis / clubbing / lymphnodes / pedal oedema / thyroid.
10. Vitals:

| | |
|-----------------------|-------------------------|
| Temp: _____ | Pulse: _____ |
| Blood Pressure: _____ | Respiratory rate: _____ |
11. Systemic examination:
 - a) Cardiovascular system.
 - b) Respiratory system.
 - c) Gastrointestinal system.
 - d) Central nervous system examination.
12. Investigations:
 - Serum glucose:
 - Serum urea:
 - Serum creatinine:
 - Serum electrolytes: sodium / potassium.
 - Serum triglyceride:
 - Serum uric acid:
 - Urine osmolality:
 - Spot urine sodium:
 - Serum osmolality:
 - T.S.H:
 - Serum cortisol:
 - HIV spot test:
 - Serum protein:
13. Radiological Examination:
 - Chest x ray (optional)
 - Ultrasound abdomen (optional)

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