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Prospective study for clinico-etiological profile of euvolemic hyponatremia among elderly patients at a tertiary care hospital in India

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Abstract:
Euvolemic hyponatremia is a common electrolyte disorder in hospitalized older adults and contributes substantially to morbidity, requiring early recognition of its clinical profile and underlying causes. This prospective observational study evaluated 100 hospitalized patients aged ≥65 years with euvolemic hyponatremia through clinical and laboratory assessment, with severity classified according to serum sodium levels. Females comprised 57%, 59% had severe hyponatremia and 18% were asymptomatic, while syndrome of inappropriate antidiuretic hormone secretion was the predominant etiology, mainly associated with respiratory diseases. Severe euvolemic hyponatremia was common, while mortality was related to underlying illnesses rather than hyponatremia and no sodium correction-related complications were observed. These findings advance knowledge by emphasizing early etiological evaluation and targeted management of euvolemic hyponatremia to improve outcomes in hospitalized older adults.

Keywords: Euvolemic hyponatremia, elderly, SIADH, serum sodium, neurological manifestations, respiratory disease

Background:
In nearly 22% of the hospitalised patients, there is one of the most significant electrolyte disturbances – Hyponatremia **[1].** It can also be categorized as hypertonic, isotonic and hypotonic depending on the serum osmolality. Once hyponatremia is determined to be hypotonic, it can further be classified as hypervolemic, euvolemic and hypovolemic hyponatremia. Hypotonic hyponatremia is then further classified as hypervolemic, euvolemic and hypovolemic hyponatremia. Patient's and health care facility's economic burden can only be seen as increased hospital length of stay, increased risk of death or disability and increased cost of care **[2].** With the help of knowledge gained through identifying etiology and risk factors for hyponatremia, decreasing the incidence of hyponatremia in hospitalized patients can help to reduce the resulting complications of hyponatremia and will help lower the cost of healthcare **[3]**. In many instances mild hyponatraemia will not cause any symptoms, but in severe cases (serum sodium concentration is less than 125 mmol/1) or when it occurs quickly (acutely less than 48 hours), cerebral oedema can occur with potentially serious neurological consequences **[4]**. Elderly correction of hyponatraemia will need to be handled carefully (there is a potential risk of quick correction resulting in the osmotic demyelination syndrome (central pontine myelinolysis)) Chronic hyponatremia patients are at greater risk for this complication **[5]**. Severe hyponatraemia has been associated with an increase in morbidity and mortality. An accurate clinical evaluation is necessary in order to provide appropriate treatment, which concentrates on any possible causes and includes the conduction of appropriate investigations, *etc.* **[6]**. Hyponatremia (Na+ < 135 mEq/L) is most frequently seen in hospitalized patients and may cause life-threatening complications such as seizures, coma and even death; assessment of this condition is difficult and treatment has often been suboptimal. This hyponatremia occurs with dehydration of the extracellular volume and is more common in the elderly primarily because their capacity for water and electrolyte balance in response to diet, medications and environmental changes is diminished **[7].** Symptoms are mostly related to central nervous system (CNS) dysfunction and are more prominent if the serum sodium level drops significantly or rapidly. In addition to neurologic symptoms, there are also non-neurologic symptoms seen like tiredness, thirst, weakness, cramping, nausea, vomiting, bloating, swelling and tightening of hands and feet. Other, mild adverse effects which are also occasionally seen in severe patients are headache, muscle cramps, reversible ataxia, psychosis, lethargy, restlessness, confusion, apathy, decreased appetite and agitation. The complications of severe and rapid onset hyponatremia can be: Seizures, coma, herniation of the brain-stem, Respiratory arrest, Permanent brain damage, Death **[8]**. Babaliche *et al.* found in a 5-year retrospective study of 2188 patients that in-intensive-care-unit (in-ICU) hyponatremia rates were 14% at admission **[9]** and Parajuli *et al.* found that in-ICU hyponatremia rates were 29.6% **[10]**. It is also known to be linked to a 60-fold rise in morbidity and mortality over patients with no evidence of hyponatraemia **[11, 12]**. Therefore, it is of interest to plan a prospective follow up study in the hospital setting in a tertiary care center as data on clinical spectrum of hyponatremia is lacking in Indian clinical settings.

Materials and Methods:
Study area:
The study was prospective study in Mata Chanan Devi Hospital in New Delhi from 2019–2021 in the Department of General Medicine and in Intensive Care Unit. Patients with serum sodium levels < 135 mEq/L was included in the study if they met the inclusion criteria and included patients ≥ 65 years of age.

Study period: 2019- 2021

Study design:
The design of study included a prospective study of 100 patients with euvolemic hyponatremia in Mata Chanan devi hospital.

Study design: Prospective cohort study.

Study objectives:
To assess the prevalence of study population (euvolemic hyponatremia elderly patients). The number of patients in the sample: 100 elderly patients with euvolemic hyponatremia.

Inclusion criteria:
[1] Patients Above 65 years of age irrespective of Gender.
[2] All cases: Euvolaemic hyponatremia (on clinical and/or biochemical parameters).
[3] All study subjects giving full informed consent for inclusion in study.

Exclusion criteria:
[1] Patients aged < 65 years
[2] Serum sodium ≥135 mEq/l
[3] Patients with isotonic, hypertonic, hypovolemic and hypervolemic hyponatremia (based on clinical, biochemical or radiological parameters)
[4] Not giving full informed consent.

Methodology:
Clinical assessment:
Detailed history:
This included history of symptoms of hyponatremia along with history of pre-existing illness. Symptomatic hyponatremia was defined on clinical judgement of symptoms such as altered sensorium, muscle cramps, lethargy/drowsiness, nausea and headache, as well as seizures. Confusional state, memory loss, stupor, delirium (not dementia), psychiatric illness and substance abuse were associated with changes in the sensorium. History of illness causing hyponatremia other than euvolemic hyponatremia such as CCF, CKD, CLD (exclusion criteria) along with those causing like hypothyroidism and other conditions which are associated with SIADH, Certain small cell cancers (small cell carcinoma), CNS disease *etc.* were collected. History of fluid loss (*e.g.,* vomit, diarrhoea, use of diuretics, excessive sweating) was asked in all patients.

History taking:
In all the patients, a detailed clinical history was taken. Clinically assessed level of hydration for patient. Signs of hypovolemia were tachycardia, decreased skin turgor and dry mucous membranes. Anasarca, ascites and bilateral pitting pedal edema were present in hypervolemic state. Patients were thus classified as hypervolemic, hypovolemic or euvolemic hyponatremia. At the time of diagnosis of hyponatremia, detailed CNS examination was done. In hyponatremia, symptoms like altered sensorium, drowsiness, headache, nausea and seizures, muscle cramps were considered to be due to hyponatremia itself, until a coexisting medical or a medication effect was identified. Patients were screened for CPM based on clinical grounds that is development of confusion, agitation and flaccid or spastic paralysis during or after correction of hyponatremia.

Investigations:
[1] RBC, Hb, TLC, Platelet count
[2] Urine routine examination and specific gravity were done.
[3] The LFTs include total bilirubin, SGOT and SGPT. LFTs include total bilirubin, SGOT and SGPT.
[4] KFT: Blood uric acid, uric acid in urine, uric acid in stool
[5] Serum sodium: Serum sodium (daily/ alternate as symptomatic/cases).
[6] The serum osmolality was determined.

The patients were subdivided into groups according to it:
[1] Isotonic - 280-295 mosm/1
[2] Hypotonic - <280 mosm/1
[3] Hypertonic - >295 mosm/1
[4] In patients with hypotonic hyponatremia (either oliguria or polyuria):
[5] Sodium- in the urine, in a patient that is hypotonic (low sodium concentration).
[6] Pressure blood tests to exclude pseudohyponatremia (first, serum protein levels and second, lipid profile).
[7] Thyroid function test, serum cortisol (if applicable).

Management and outcome assessment:
The patients with hyponatremia were categorized according to the serum sodium level into following Categories:
[1] Mild 130-135 mEq/1
[2] Moderate 125-129mEq/l
[3] Severe<125 mEq/1

SIADH diagnostic criteria - The diagnostic criteria used were as described by Verbalis-(13)

Essential criteria:
[1] Osmolality of the effective osmotic component of extracellular fluid (ECF) that is < 270 mOsm/kg water.
[2] Inappropriate urinary concentration (>100 mOsm/kg).
[3] Absence of signs of hypovolemia and hypervolemia (clinical euvolemia)
[4] Increased urinary (Na+) while on a normal salt and water intake.
[5] No adrenal, thyroid or pituitary deficiency or taking diuretics.

Supplemental criteria:
[1] Abnormal water load test: unable to pass a 20ml/kg water load in 4 hours and/or urinary osmolality not below 100mOsm/kg).
[2] Plasma AVP level inappropriately raised as compared to plasma osmolality.
[3] No significant correction in plasma (Na+) with volume expansion; but improvement after fluid restriction.

The assessment of the outcomes and the management of them.
Based on serum sodium level, patients with hyponatremia were classified into the following Categories:
(i) Mild hyponatremia – 131 – 134 mEq/L
(ii) Moderate hyponatremia – 125 – 130 mEq/L
(iii) Severe hyponatremia – <125 mEq/L

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Treatment strategy:
Decision on the treatment modality was based on the cause, severity of hyponatremia and presence of neurological symptoms of hyponatremia.

Data collection:
The clinical and demographic data, final diagnosis, investigations and outcome of all patients was recorded on a standard patient data collection sheet as per study proforma and entered into the patient record in Microsoft excel and subsequently analysed.

Ethical consideration:
The ICMR guidelines were followed. Information about personal information in research within the medical field. Approval from Ethical committee and the Scientific Research Committee was taken to perform the study. In all cases, written informed consent was also obtained (in bilingual language) and data was obtained from the study patient after obtaining consent.

Data entry and statistical analysis:
The quantitative variables are presented as Mean ± SD and compared between the groups using Mann-Whitney and unpaired t-test and Anova test. Qualitative variables are compared between groups using Chi-square test. The statistical significance is accepted as p value < 0.05. Data was shared in MS Excel spreadsheet and IBM Statistical Package for Social Sciences (SPSS) version 20.0 was used to analyze data.

Results:
The maximum numbers of patients were in the age group 65–75 years. Of patient's 11% were more than 85 years old and 41% was from the age group of 76–85 years. Number of patients in different as groups are shown in **(Table 1)**. In this study out of 100 euvolemic patients 43 were female and 57 were male. Most 82 had symptoms at presentation. For symptomatic cases, some of the patients were having more than one symptom. 45 patients were drowsy, 43 had altered sensorium, due to hyponatremia, 38 were lethargic, 33 were written as a patient with nausea and 25 patients complained of headache. Among patients, 9 complained of muscle cramps and 4% of the patients were having seizure. 18% of the patients in our study were asymptomatic **(Table 2)**. Out of 100 cases of euvolemic hyponatremia majority 59% were having severe hyponatremia, 18% had moderate and 23% were having mild hyponatremia **(Table 3).** Out of 100 cases most common aetiology of euvolemic hyponatremia was SIADH found in 55% of the patients. The majority (28%) had hypothyroidism, with 6% having exercise induced and 4% the primary polydipsia. 1 of the patients had adrenal insufficiency. 6% of the cases had other causes like reset Osmostat **(Table 4)**. Most of the cases of SIADH were due to drugs accounting for 41.82% of the SIADH cases. About 31% cases of SIADH were due to respiratory infections and pneumonia was the significant aetiology. Central nervous system insult with central venous circulation affecting as the major aetiology accounted for about 15% of the cases of SIADH. 2 of the patients had SIADH due to malignancy and 4 of the patients were due to non-osmotic stimuli **(Table 5)**.

Table 1: Age distribution (n = 100)

Age (years)	n
65 – 75	48
76 – 85	41
>85	11
TOTAL	100

Table 2: Symptoms of the participants at presentation (n = 100)

Symptoms	n
Altered Sensorium	43
Drowsy	45
Headache	25
Lethargy	38
Nausea	33
Seizure	4
Muscle Cramps	9
Asymptomatic	18

Table 3: Severity of hyponatremia

Severity	n
Mild	23
Moderate	18
Severe	59
TOTAL	100

Table 4: Aetiology of hyponatremia

Cause	n
ADI	1
Exercise Induced	6
Hypothyroidism	28
Others	6
Primary Polydipsia	4
SIADH	55

Table 5: Aetiology of SIADH

EOS for SIADH	n	%
CAPan	1	1.82%
CAPr	1	1.82%
COPD	6	10.91%
Cerebro Vascular Accident	5	9.09%
Drug	23	41.82%
Guillain-Barré syndrome	1	1.82%
Meningitis	2	3.64%
Meningitis/PTB	1	1.82%
Non-Osmotic Stimuli	4	7.27%
Pneumonia	10	18.18%
Pneumothorax	1	1.82%
TOTAL	55	100%

Discussion:
Hyponatremia is an important electrolyte abnormality among older hospitalized patients because advancing age is accompanied by reduced renal reserve, impaired water handling, multiple comorbidities and frequent exposure to medications that influence sodium balance. It may also adversely affect the clinical course and prolong hospitalization. Rajendram *et al.* **[12]** showed that admission hyponatremia was associated with unfavorable hospital outcomes among medical patients, emphasizing the clinical relevance of early recognition and appropriate management. In the present study, 100 patients aged ≥65 years were evaluated, comprising 43% males and 57% females. Nearly half of the participants (48%) belonged to the 65–75-year age group, followed by 41% aged 76–85 years and 11% aged >85 years. Although hypothyroidism was identified in 28% of patients, the relationship between thyroid dysfunction and hyponatremia requires cautious interpretation. Chen **[13]**

highlighted that clinically important hyponatremia cannot always be attributed directly to hypothyroidism, particularly in the absence of severe thyroid dysfunction and other contributing causes should therefore be considered. Most patients (82%) were symptomatic. Drowsiness (45%), lethargy (43%) and altered sensorium (38%) were prominent manifestations, while nausea (33%), headache (25%), muscle cramps (19%) and seizures (4%) occurred less frequently. These findings are broadly consistent with the clinical spectrum reported by Sood *et al.* **[14],** who described neurological and constitutional manifestations as common presentations of hyponatremia. Symptoms may vary considerably according to the severity and rate of decline in serum sodium because gradual hyponatremia permits cerebral adaptation and may consequently produce few or no manifestations. Severe hyponatremia constituted the largest category in the present study (59%), whereas 23% had mild and 18% had moderate hyponatremia. Interestingly, 18% of patients were asymptomatic, with most of these individuals having mild sodium reduction. Jain and Nandy **[15]** similarly observed considerable variation in clinical presentation among elderly patients with hyponatremia, indicating that serum sodium concentration and clinical manifestations do not always show a uniform relationship. SIADH was the predominant etiology, accounting for 55% of cases, followed by hypothyroidism (28%). Respiratory disorders were present in 54.5% of patients with SIADH and pneumonia was the leading probable precipitating factor. Chandregowda *et al.* **[16]** also identified SIADH as an important cause of hyponatremia among elderly medical inpatients, although the underlying disorders varied according to the patient population and local disease pattern. Somendra and Sharma **[17]** similarly identified SIADH as an important aetiology, particularly in patients with tubercular meningitis, while hypovolemic hyponatremia was the most common overall type, frequently associated with sepsis. Collectively, these observations indicate that hyponatremia in older adults is frequently multifactorial and that evaluation should include assessment for pulmonary disease, neurological disorders, endocrine abnormalities, medications and disturbances of fluid balance. The present study was limited by its single-center design and relatively small sample size. Nevertheless, the findings show that hyponatremia in elderly hospitalized patients commonly presents with neurological or nonspecific symptoms, with severe hyponatremia and SIADH forming a considerable proportion of cases. Careful etiological assessment and timely correction of sodium disturbances may therefore contribute to improved clinical management in this vulnerable population.

Conclusion:

Severe euvolemic hyponatremia was common among hospitalized older adults, with neurological manifestations predominating, while mild hyponatremia was frequently asymptomatic. Syndrome of inappropriate antidiuretic hormone secretion, primarily secondary to respiratory diseases, was the leading cause, emphasizing the importance of identifying the underlying etiology rather than focusing solely on serum sodium correction. Thus, data support a systematic diagnostic approach integrating clinical assessment and laboratory evaluation to optimize the management of euvolemic hyponatremia in elderly patients.

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