

## Original Article

# Study of Neurologic Manifestations of Hyponatremia with Special Reference to Unusual Rare Manifestations

Nishtha Jain<sup>1</sup>, Vijay Sardana<sup>2</sup>, Dilip Maheshwari<sup>3</sup>, Bharat Bhushan<sup>4</sup>, Sunil Kumar Sharma<sup>5</sup>

**Background :** The normal serum sodium concentration ( $[Na^+]$ ) in the human body ranges from 135 to 145 mEq/L and is maintained by renal mechanisms. A serum  $[Na^+]$  less than 135 mEq/L is usually defined as hyponatremia. A significant hyponatremia can lead to various neurologic manifestations. Overcorrection of hyponatremia can lead to neurological deterioration secondary to Osmotic Demyelination Syndrome (ODS). This study was done to see the various neurologic manifestations in patients with hyponatremia and to study outcome after treatment.

**Objective :** The objective of this study is to evaluate the common and rare neurological effects of hyponatremia and to correlate them with different range of serum sodium levels and also to study the outcomes including recovery and adverse effects after correction. Differences in the neurological manifestations of hyponatremia in young (<50 yrs) and old (>50yrs) patients were also studied.

**Methods :** 200 patients were included who were admitted with symptomatic hyponatremia.

**Results :** Mean age of presentation of patients was 63.89 years. Most of the patients were having comorbid conditions which included Hypertension, Diabetes Mellitus, Hypothyroidism, Chronic Liver Disease, Chronic Renal Disease, Epilepsy, Schizophrenia, Coronary Artery Disease, Stroke and Rheumatoid Arthritis. The neurologic manifestations of the patients included encephalopathy, followed by extrapyramidal features, generalised tonic clonic seizures, ataxia and focal seizures. Rare manifestations included ataxia and focal seizures. A strong association between sodium levels <120 meq/l and generalised tonic clonic seizures as presentation was found. ODS was observed in seven patients.

**Conclusion :** Hyponatremia is very frequent in elderly. It is mostly associated with multiple comorbid conditions and can present with varying manifestations. Proper recognition of the condition is important as it is a potential treatable condition.

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**Key words :** Hyponatremia, Comorbidities, Neurologic manifestations, Adverse effects.

The normal serum sodium concentration ( $Na^+$ ) in the human body ranges from 135 to 145 mEq/L and is maintained by renal mechanisms that regulate the excretion of water<sup>1</sup>. Abnormality of water excretion and intake, or, less often, an rise in urinary sodium excretion will raise the body water content relative to the body sodium content, thereby reducing the serum ( $Na^+$ ). A serum ( $Na^+$ ) less than 135 mEq/L is usually defined as hyponatremia<sup>1</sup>. The disorder occurs in 15 to 22% of hospitalized patients and is the most common fluid-electrolyte disorder among hospitalized patients<sup>2</sup>.

Hyponatremia is divided in three Groups, viz: (i) mild hyponatremia: it is defined as serum sodium level between 130 - 135 mmol/L; (ii) moderate hyponatremia: it is defined as serum sodium level between 125-130 mmol/L and severe hyponatremia: it is defined as serum sodium level less than 125mmol/L<sup>3</sup>.

Water gain due to hypotonicity leads to swelling of the brain. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation). The normalization of brain volume occurs through loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the

Department of Neurology, Government Medical College, Kota 324001

<sup>1</sup>DM Resident (Neurology), Senior Resident and Corresponding Author

<sup>2</sup>DM (Neurology), Senior Professor and Head

<sup>3</sup>DM (Neurology), Associate Professor

<sup>4</sup>DM (Neurology), Professor, Department of Medicine, Government Medical College, Kota 324010

<sup>5</sup>DM Resident (Neurology), Senior Resident

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### Editor's Comment :

- Symptomatic hyponatremia is mostly prevalent among the elderly.
- Presence of comorbidities is an important determinant.
- Commonest neurological manifestation is encephalopathy and seizures are common when sodium level is less than 120 meq/l.
- Gradual correction is the norm to avoid Osmotic Demyelination Syndrome (ODS).

brain persists despite the normalization of brain volume. Normal osmolality is restored by correction of hypotonicity risking damage to the brain. Too rapid correction of hyponatremia can lead to irreversible brain damage. Therefore correction of hyponatremia must take into account the chronicity of the condition. Acute hyponatremia (duration less than 48h) can be safely corrected more quickly than chronic hyponatremia<sup>4</sup>.

Patients with mild hyponatremia (plasma sodium 130-135 mmol/L) of any duration are usually asymptomatic. Nausea and malaise are the earliest symptoms. Headache, restlessness and disorientation occurs as the sodium concentration falls below 115-120 mmol/L. With severe and rapidly evolving hyponatremia, seizures, coma, permanent brain damage, respiratory arrest, brain stem herniation and death may occur.

Hyponatremia is important to recognize because of the common occurrence and potential morbidity and mortality. The economic impact of hyponatremia on the patient and the health care facility is evident by longer duration of stay, higher risk of death and disability

and increased cost of care.

So this study is planned to be carried out in all the patients with symptomatic hyponatremia and to focus on the rare neurologic manifestations attributable to it and observe the outcomes including recovery and adverse effects which can be helpful to recognise the rarer manifestations caused by it and to see the correlation between the sodium levels and the severity of manifestations for making further protocol for management of hyponatremia. There has been many studies on hyponatremia in the geriatric population but there is not much literature available in young patients and also there are no studies comparing the manifestations and adverse effects of hyponatremia in young patients (<50 years) and old patients (>50 years). So in this study we will also focus on the differences, if any, in the neurological manifestations of hyponatremia and outcome of correction between young (<50yrs) and old (>50 yrs) patients.

#### AIMS AND OBJECTIVES

The objective of this study is to evaluate the common and rare neurological manifestations of hyponatremia and to correlate them with different range of serum sodium levels and also to study the outcomes including recovery and adverse effects after correction. Differences in the neurological manifestations of hyponatremia in young (<50 yrs) and old (>50yrs) patients were also studied.

#### MATERIALS AND METHODS

This study was conducted in the Department of Neurology for a period of one year (2017- 2018) after getting clearance from ethical committee. 200 patients were included from adults admitted with symptomatic hyponatremia. All patients were included after written informed consent. Patients with symptomatic hyponatremia were given intravenous infusion of hypertonic saline, in order to increase of 6 mmol/L over 24 hours (not exceeding 12 mmol/L) and 8 mmol/L during every 24 hours thereafter to bring sodium level to 130 mmol/L. The following equation was used to gauge an expected change in serum sodium (Na) with respect to characteristics of infusates used: Change in serum Na = [(infusate Na + infusate K) - serum Na] / [Total body water +1] Close monitoring of serum electrolytes (ie, every 2-4 h) to avoid overcorrection was done.

**Inclusion Criteria** — Patients above 18 yrs of age with serum sodium levels < 130 meq/l presenting with neurological complaints were included in this study.

**Exclusion Criteria** — Patients with abnormal Cerebrospinal Fluid (CSF) examination, any structural cause found responsible for the neurological condition, chronic liver disease (Grades B and C according to Child-pugh classification), Glomerular filtration rate (GFR) below 10% of normal<sup>5</sup> and any other metabolic abnormality eg, hypoglycemia which can

cause similar clinical manifestations.

**Statistical Analysis** — The categorical variables were compared by Chi-square test. The t-test was used to compare the variables between the two groups. The p-value<0.05 was considered significant. All the analysis was carried out on Statistical Package for the Social Sciences (SPSS) 20.0 version.

#### RESULTS

During the study period, a total 200 patients of symptomatic hyponatremia were enrolled after considering the inclusion and exclusion criteria mentioned above. Patients were treated according to the treatment protocol described and the serum sodium levels were closely monitored.

The maximum number of patients were above 50 years of age. Mean age of presentation was 63.89 years. Majority of patients in the study population were males (60.5%).

Most of the patients (76.5%) were having various comorbid conditions which included Hypertension (61.5%), Diabetes Mellitus (28.5%), Hypothyroidism (5.5%), Chronic Liver Disease (4%), Chronic Renal Disease(6.5%), Epilepsy (1.5%), Schizophrenia (2%), Coronary Artery Disease (9.5%) and Stroke (19.5%) and Rheumatoid Arthritis (1%).

The mean serum sodium levels at the time of admission were 121.40 meq/l, the minimum level being 90 meq/l and the maximum level was 130 meq/l at presentation. 34% patients had serum sodium of 126-130 meq/l at presentation, 35% had 120-125 meq/l at presentation while 31% patients had serum sodium levels of <120 meq/l at the time of admission. The neurologic manifestations of the patients included encephalopathy (86%), followed by extrapyramidal features in form of rigidity and bradykinesia (10%), generalised tonic clonic seizures (9.5%), ataxia (4%) and focal seizures (1%). The frequency distribution of the various neurologic symptoms according to Serum Sodium levels and age is shown in Fig 1 and 2 respectively.

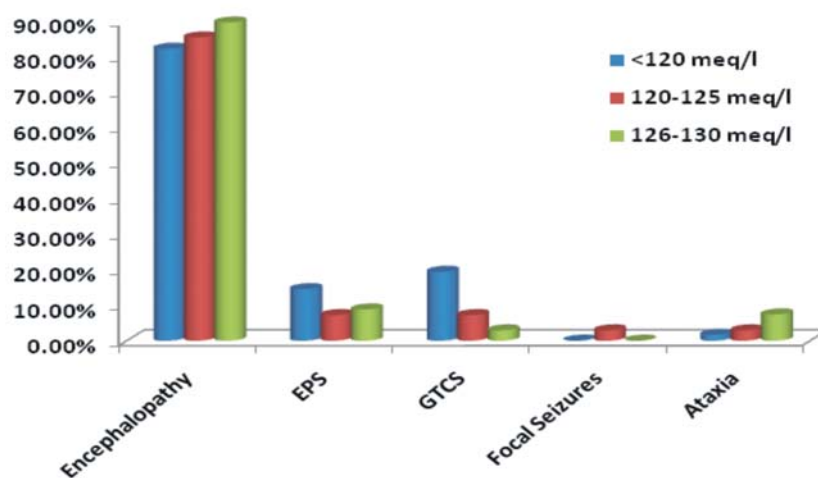


Fig 1 — Distribution of various neurologic manifestations at different Serum Sodium levels  
EPS- Extrapyramidal symptoms, GTCS- Generalised Tonic Clonic Seizures

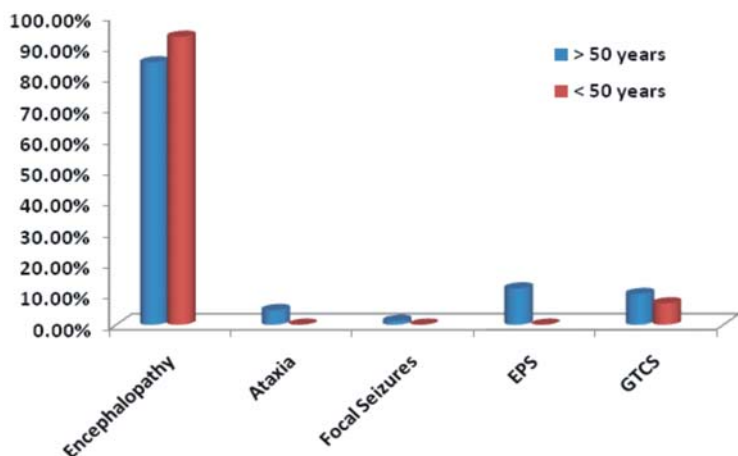


Fig 2 — Distribution of Various Neurologic Manifestations According to Age Distribution.

EPS - Extrapyramidal symptoms, GTCS - Generalised Tonic Clonic Seizures

As far as the neurologic manifestations are concerned, there was no statistically significant difference found between the patients who were less than 50 years of age when compared to the patients older than 50 years (Table 1).

When the association between the serum sodium levels at admission with neurologic manifestations at admission were compared, a strong association between sodium levels <120 meq/l and generalised tonic clonic seizures as presentation was found. No other neurologic manifestation was found to have any association

Table 1 — Distribution of various neurologic manifestations according to age distribution

Neurologic Manifestation	Patients >50 years (%)	Patients <50 years (%)	P value
Ataxia	4.7	0	0.235
Focal Seizures	1.2	0	0.558
Encephalopathy	84.8	93.1	0.233
Extrapyramidal symptoms	11.7	0	0.052
GTCS	9.9	6.9	0.605

GTCS- Generalised Tonic Clonic Seizures.

Table 2 — Distribution of Various Neurologic Manifestations According to Serum Sodium Levels at Admission

Neurologic manifestation	Mean Sodium levels without concerned manifestation (meq/l)	Mean Sodium levels with concerned manifestation (meq/l)	P value
Ataxia	121.24	125.12	0.121
Focal Seizures	121.40	121.00	0.935
Encephalopathy	119.11	121.77	0.059
Extrapyramidal symptoms	121.42	121.20	0.892
GTCS	122.01	115.58	<0.001*

GTCS - Generalised Tonic Clonic Seizures.

\* - Statistically significant

with range of serum sodium levels (Table 2).

Seven patients developed adverse effects of treatment given in form of ODS which was found secondary to faster rate of correction of serum sodium levels and most of these patients were referred from the peripheral centres after neurological deterioration. Five of these patients had involvement of pons and two had involvement of basal ganglia and presented with extrapyramidal symptoms. The distribution of the neurological side effects seen is shown in Fig 3.

**DISCUSSION**

This was a prospective observational study carried out in the patients admitted with symptomatic hyponatremia with neurologic manifestations. A total of 200 patients were enrolled during the study period and were observed for neurologic symptoms attributable to hyponatremia and also for recovery and adverse effects.

We have enrolled the patients with hyponatremia under three categories on the basis of serum sodium levels ie, <120 meq/l, 120-125 meq/l and 126-130 meq/l. Patients with levels more 130 meq/l were not enrolled as most of these were not having any neurologic manifestations at presentation. We also divided the study population according to age (more than or less than 50 years) for assessing any correlation between age of presentation and neurologic manifestation.

The most common neurologic manifestation seen in the study population was encephalopathy followed by extrapyramidal symptoms, GTCS, Ataxia and focal seizures. Patients with serum sodium levels less than 120 meq/l were found to have more propensity to have GTCS as compared to patients with higher serum sodium levels at presentation. There was no statistically significant difference found between serum sodium levels and any other neurologic manifestation. Most of the patients in the study were older than 50 years of age with multiple comorbidities. The various comorbidities may predispose the patients to hyponatremia by decreasing oral intake or because of certain medications prescribed such as diuretics, antiepileptics etc.

There was no statistically significant difference found between the neurologic manifestations of patients who were less than 50 years of age when compared to the older population. Seven of the patients developed adverse effects attributed to the correction of sodium levels in the form of osmotic demyelination syndrome involving pons in five and basal ganglia in two patients. Most of these patients were referred from primary care physicians after deterioration in neurological status, so it may possible that they did not follow the proper treatment protocol for sodium correction.

There has been many studies for evaluating the patients of hyponatremia. In a study by Nankabirwa *et al*, the patients enrolled were older than 60 years of age and were having heart failure who were taking loop diuretics. The most common symptoms in the study were falls, altered behaviour and mentation and the risk

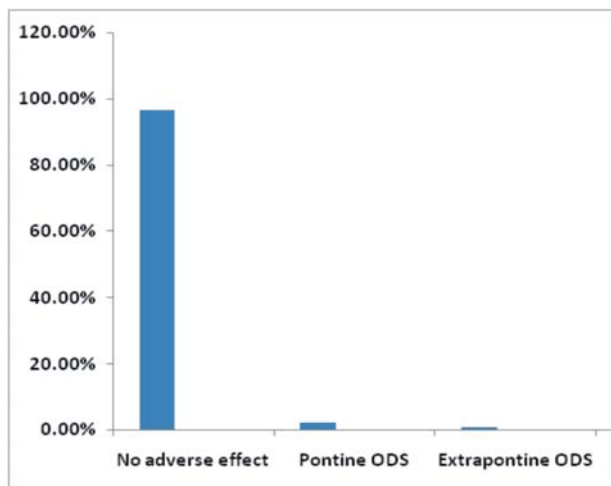


Fig 3 — Frequency distribution of adverse effect in the study population  
ODS- Osmotic Demyelination Syndrome

factors most commonly associated included hypertension and heart failure. In the present study also most of the patients were more than 50 years of age and were having hypertension as the most common comorbidity with encephalopathy as the most common neurologic manifestation.

In a study by Rao *et al*<sup>7</sup>, 100 patients with symptomatic hyponatremia were studied. Most frequent symptoms included drowsiness, lethargy, confusion, seizures and coma. The co-morbid conditions associated were Hypertension (69%) and diabetes mellitus (51%). The common cause of Hyponatremia was Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) followed by drugs of which diuretics was the main culprit.

In a study by Patil *et al*<sup>8</sup>, it was concluded that hyponatremia is most common in critically ill patients admitted to ICU. Most etiological factors involved in it are severe sepsis, renal failure, liver cirrhosis, trauma, hypothyroidism, and hypocortisolism. Neurological manifestations include seizures, reduced consciousness level, confusion, unsteadiness, and falls.

In a study by Paniker *et al*<sup>9</sup>, a total of 100 patients were included. The mean age of patients in the study was 55.05 years. The most common neurologic symptoms included confusion, tremors, hallucinations, seizures, psychosis, coma. In this study the authors have also seen the manifestations at different serum sodium levels. Seizures were noted in moderate to severe hyponatremia. In the present study also we found that the seizures were more common in patients with lower levels of serum sodium levels.

Similar results were seen in study by Gopinath *et al*<sup>3</sup>. Among the 50 patients with hyponatremia, 42% of encephalopathy patients had metabolic encephalopathy. Majority who developed hyponatremia had age between 61 to 80 years. Clinical profile of patients with hyponatremia was revealed and most of the patients with hyponatremia were observed having confusion followed by nausea/vomiting, delirium, seizure. The common co-morbid conditions for hyponatremia were hypertension 55.93%, diabetes mellitus 43.85%, and chronic renal failure 35.29%.

Similar to all these studies, the present study also showed the association of hyponatremia with multiple comorbidities and old age. Also the most common neurologic manifestation was encephalopathy and the incidence of seizures increased with decrease in serum sodium levels. But in none of the previous studies the comparison was done between the patients of age less than and more than 50 years. Also extrapyramidal symptoms were not described as major neurologic manifestation in any of the previous studies. Along with in none of the studies the frequency of adverse effects with correction of hyponatremia was studied.

### CONCLUSION

Hyponatremia is a common dyselectrolytemia disturbance seen in the elderly. It is mostly associated with multiple comorbid conditions associated with decreased oral intake and multiple medications. Proper recognition of the condition is important as it is potential treatable condition with very less incidence of adverse effects secondary to treatment and if left untreated will lead to serious neurologic outcomes. Primary care physicians should be educated regarding the protocol of sodium correction in cases of hyponatremia so that incidence of ODS can be reduced.

**Source of Support :** Nil

**Conflicting Interest :** None

**Ethical Clearance :** Ethical clearance was obtained from the Institutional Ethics Committee.

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