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Original Research Article

A Clinical Profile of Hyponatremia in Stroke Patients in a Tertiary Care Hospital

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ABSTRACT

Background
This study was conducted to evaluate the clinical profile of hyponatremia in stroke patients and to compare and contrast between SIADH (Syndrome of Inappropriate Secretion of Antidiuretic Hormone) and CSWS (Cerebral Salt Wasting Syndrome) based on the results.

Methods
This was a hospital based single center, descriptive type of cross-sectional study considering the prevalence of hyponatremia in stroke patients to be 35%, based on the estimation of proportion, in the Department of General Medicine, Department of Neurology, at Kasturba Hospital, Manipal a unit of Kasturba Medical College, Manipal, MAHE (Manipal Academy of Higher Education) over a period of 1.5 years from 01/01/2021 to 31/07/2022 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results
The mean sodium value in the hyponatremia group was 131±3.6 mEq/L, with the lowest value being 119 mEq/L and the upper limit being 135 mEq/L. Patients with hyponatremia had a statistically significant ($p = 0.05$) prevalence of headache as compared to controls. The prevalence of hypertension (70.5%) and IHD (ischemic heart disease) (20.5%) was higher in the control group. A statistically significant ($p = 0.034$) number of patients in the CSWS group (64.7% and 58.8%) had headache and altered sensorium, respectively, which was more as compared to SIADH. Comorbidities were compared amongst patients with SIADH and CSWS, and 53.3% of SIADH patients had diabetes mellitus, 66.7% had hypertension and 20% had IHD, which were slightly more than those of CSWS, respectively. Further classifying SIADH and CSWS patients based on stroke subtypes, it was observed that a significant number of patients (11.8%) of CSWS had hemorrhagic strokes than SIADH patients (3.3%). Thrombotic strokes dominated both groups. Major laboratory parameters were tabulated amongst patients with SIADH and CSWS, and it was observed that serum uric acid levels were lower (4.1±0.92) for SIADH as compared to CSWS, which was statistically significant ($p = 0.02$), and that urine

sodium levels were higher (99±5.2) for CSWS patients than for SIADH, which was statistically significant.

Conclusion

Patients with hemorrhagic stroke are more likely to have CSWS, as compared to SIADH. In the setting of true hyponatremia in stroke patients, a higher urinary sodium level and a normal-high uric acid level were likely to be CSWS.

Keywords: Hyponatremia, Stroke Patients.

INTRODUCTION

Stroke is defined as a sudden onset of focal neurological deficit that is attributable to a vascular etiology.[1] It causes disabling neurological illness, and it is one of the foremost causes of morbidity or functional loss. In India, the incidence of stroke is higher when compared to western countries.[2] By definition, hyponatremia means a serum sodium level of ≤135 mmol/L.[3] Hyponatremia is a frequently seen electrolyte abnormality in patients of neurological disorders such as stroke, meningitis, and subarachnoid hemorrhage; which is usually either due to SIADH (Syndrome of Inappropriate Secretion of Antidiuretic Hormone) or CSWS (Cerebral Salt Wasting Syndrome).[4] Reports suggest that hyponatremia accounts for 3-5% of inpatients, while the incidence in neurological patients has been reported to be as high as 50%.[5] It resulted in higher mortality, hospital costs, readmission rates and longer hospital stays.

SIADH is a condition defined by the "unsuppressed" release of ADH from the pituitary gland or extra-pituitary sources, or its continued action on Vasopressin receptors. It is characterized by "inappropriately" concentrated urine, high urine osmolality, and low sodium levels when other etiologies for hyponatremia have been ruled out. In SIADH, there is euvolemic hyponatremia, and loss of the negative feedback system, thus leading to an excess release of ADH from the posterior pituitary. Many CNS (Central Nervous System) diseases are associated with SIADH. Stroke, infection, trauma, hemorrhage and psychosis all enhance ADH release. The classic description of the CSWS includes excessive sodium excretion in the urine (natriuresis) and resultant water loss and dehydration. Hence it leads to low sodium levels and is seen to occur most commonly in patients with central nervous system diseases. In CSWS, there is a reduction in the blood volume. Due to the low sodium levels, there is a reduction in the effective osmolality of the plasma, and hence, to adapt to this change, water moves into the brain cells, leading to cerebral edema. Hence, hyponatremia is an important established cause of mortality and future morbidity in CVA (Cerebrovascular Accidents). Timely treatment is very effective and can decrease mortality significantly. However, studies showing the extent of dyselectrolytaemia in CVA patients are rare from India. Due to the above reasons, the above disorders of euvolemic hyponatremia like SIADH and CSWS (that have a low blood volume with low sodium levels) must be differentiated. This is necessary because their management strategies vary. There is a paucity of data in this regard, more so from the rural population, and only a few exhaustive studies have been done on cerebrovascular accidents and their resultant metabolic changes. Hence, this study aims to elaborate on the clinical profile of hyponatremia in stroke patients and compare and contrast between SIADH and CSWS based on the results.

AIMS AND OBJECTIVES

- To determine the incidence, clinical profile, and etiology of hyponatremia in newly diagnosed stroke patients (cerebrovascular accident).
- To classify patients with hyponatremia according to the type of stroke (ischemic/hemorrhagic) and anterior/posterior circulation and comorbidities.

- To find out the severity of hyponatremia in strokes and its relation to the disease.

MATERIALS & METHODS

This was a hospital-based single-center, descriptive type of cross-sectional study considering the prevalence of hyponatremia in stroke patients to be 35%, based on the estimation of proportion, to the Department of General Medicine, Department of Neurology, at Kasturba Hospital, Manipal. A unit of Kasturba Medical College, Manipal, MAHE (Manipal Academy of Higher Education) over a period of 1.5 years from 1st January 2021 to 31st July 2022 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Patients >18 years of age
- Based on history, clinical examination, and radiological findings (either CT scan (Computed Tomography) or MRI (Magnetic Resonance Imaging), diagnosed as acute stroke, who present within 48 hrs. of stroke onset
- Who had not received any anti-cerebral edema measures (like diuretics, steroids, or mannitol) before presenting to the hospital

Exclusion Criteria

- Patients with recurrent stroke or residual paralysis.
- Patients with a h/o head trauma.
- Patients with any coexisting infection, e.g., bacterial pneumonia, pulmonary TB (Tuberculosis), or evidence of CNS (Central Nervous System) infection-meningitis, encephalitis.
- Patients with renal failure or CKD (Chronic Kidney Disease).
- Patients with liver failure or chronic liver disease.
- Patients with CCF (Congestive Cardiac Failure).
- Patients with any malignancy, e.g., bronchogenic carcinoma, leukemias.
- Patients with a h/o any surgery within the last 3 months.
- Patients with a h/o gastroenteritis and diarrhea.
- Patients taking any drugs that cause hyponatremia, e.g., diuretics, carbamazepine, fluoxetine.
- Patients with serum glucose >300 mg/dl or TG >400 mg/dl.
- H/o any monoclonal gammopathy/MDS/amyloidosis/IvIG (intravenous immunoglobulin) therapy.
- Patients with any pre-existing thyroid disease.

Data Collection

1. For all patients that fit the inclusion criteria, informed consent was taken
2. History-taking was done in detail for any comorbidities, time since stroke event, clinical features, and drugs and medications used before admission, and entered into a standardized proforma made for all Both cases and controls were taken from the time of admission from the OPD/Emergency until the initial investigations were sent.
3. A complete physical examination, especially a neurological examination was done.
4. Based on the CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) findings, diagnosed as acute stroke.
5. Based on the type of stroke on CT or MRI, patients were classified into ischemic strokes

and hemorrhagic strokes.

6. NIHSS stroke scale (National Institute of Health Stroke Scale) was calculated for all these patients, and severity of stroke was graded as per the above scale.
7. Each stroke patient was further classified into anterior circulation and posterior circulation based on vascular territory and area of the brain involved in stroke, as per their CT angiography or MR angiography images.
8. For differentiation between pseudo- and true hyponatremia, serum osmolality was Serum osmolality <275 mOsm/kg and a serum sodium <125 mEq/Litre constitute true hyponatremia.
9. For patients with true hyponatremia, investigative workup, including serum osmolality, urine osmolality, urine spot sodium, random cortisol, urine specific gravity, and uric acid, was sent to find out the etiology of hyponatremia.
10. Causes of hyponatremia were classified into SIADH, CSWS, and other causes based on the results.
11. Institutional ethical committee clearance was received (IEC: 49/2021), and CTRI registration was done before starting any
12. The following parameters were recorded:
    - Age and Gender
- Mode of presentation
- Comorbid conditions: COPD (Chronic Obstructive Pulmonary Disease)/bronchial asthma, diabetes mellitus, ischemic heart disease, and hypertension.
- CT scan, MRI reports and angiographic reports regarding type of stroke and area/vessel.
- Biochemical parameters as mentioned above.

Sample Size

Considering the prevalence of hyponatremia in stroke patients to be 35%, based on the estimation of proportion, the sample size was **100** at 10 percent margin of error.

Using the formula:

$n = N*X / (X + N - 1)$,

Where,

$X = Z\ \alpha/2\ 2\ *p*(1-p) / MOE\ 2$, and $Z\ \alpha/2$ is the critical value of the normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), MOE is the margin of error, p is the sample proportion, and N is the population size.

Statistical Methods

Results are presented as mean, SD, and range values for continuous data and frequencies as numbers and percentages. An unpaired t-test was used to compare the means of two groups. Categorical data was analyzed by the chi-square test. A p-value of 0.05 or less was considered for statistical significance. SPSS (Version 17, IBM) software was used for data analysis. All the data was entered and tabulated in Microsoft Excel before analysis. Descriptive statistics are given by frequency tables, percentages, and using mean and standard deviation wherever necessary.

RESULTS

Sodium Level in Patients with Hyponatremia		
	Hyponatremia (n=56)	**Significance**
Mean	131.8	**t = 11.45, P < 0.001, HS**
SD	3.6	

Range	119 - 135	-	
t: Unpaired t test			
*** P < 0.001, High Sig.**			
Sodium Level in Patients with Hyponatremia			
Sodium Level in Patients without Hyponatremia			
	No Hyponatremia (n=44)	**Significance**	
Mean	138.8	**t = 12.55, P < 0.001, HS**	
SD	2.1		
Range	136 - 144	-	
t: Unpaired t test			
*** P < 0.001, High Sig.**			
Sodium Levels in Patients without Hyponatremia			
Table 1			

The mean sodium value in the hyponatremia group was 131±3.6 mEq/L, with the lowest value being 119 mEq/L and the upper limit being 135 mEq/L.

Involvement	**No Hyponatremia (N = 44)**		**Hyponatremia (N = 56)**		**Total (N = 100)**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Paraplegia	4	9.1	2	3.6	6	6.0
Left or Right Hemiplegia/Hemiparesis	35	79.5	48	85.7	83	83.0
No Motor Deficits	5	11.4	6	10.7	11	11.0
Total	44	100.0	56	100.0	100	100.0
X^2 = 1.38, P = 0.71, NS						
Motor Involvement Compared between the Hyponatremia and Control Groups						

Co-Morbidities		**No Hyponatremia (n = 44)**		**Hyponatremia (n = 56)**		**Total (n = 100)**		**Significance**	
		No.	**%**	**No.**	**%**	**No.**	**%**	**X^2**	**P**
Diabetes	Yes	23	52.3	30	53.6	53	53.0	0.02	0.9
	No	21	47.7	26	46.4	47	47.0		
Hypertension	Yes	31	70.5	38	67.9	69	69.0	0.08	0.78
	No	13	29.5	18	32.1	31	31.0		
IHD	Yes	9	20.5	10	17.9	19	19.0	0.11	0.74
	No	35	79.5	46	82.1	81	81.0		
BA/COPD	Yes	1	2.3	1	1.8	2	2.0	0.03	0.86
	No	43	97.7	55	98.2	98	98.0		
Chi-square test									
* P < 0.05, Sig.									
P > 0.05, Not Sig.									
Associated Co-Morbid Conditions assessed between the Hyponatremia Group and Control Group									
Table 2									

In our study cohort, major clinical features were compared between the hyponatremia group and controls. with 89% of the patients with hyponatremia having motor deficit, 91.1%

having cranial nerve involvement, 35.7% having altered sensorium, and 62.5% having headache. Patients with hyponatremia had a statistically significant (p = 0.05) prevalence of headache as compared to controls.

Our study showed that diabetics were more prevalent (53.6%) in the hyponatremia group than the controls, whereas the prevalence of hypertension (70.5%) and IHD (ischemic heart disease) (20.5%) was higher in the control group.

Clinical Features Among Stroke Patients with Hyponatremia (N = 56)											
Clinical features		**SIADH (n=30)**		**CSWS (n=17)**		**Others (n=9)**		**Total (N=56)**		**Significance**	
		No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**X^2**	**P**
Motor Deficit	Yes	26	86.7	15	88.2	9	100.0	50	89.3	1.32	0.52
	No	4	13.3	2	11.8	0	0.0	6	10.7		
Cranial Nerves	Yes	28	93.3	14	82.4	9	100.0	51	91.1	2.66	0.26
	No	2	6.7	3	17.6	0	0.0	5	8.9		
Headache	Yes	18	60.0	11	64.7	6	66.7	35	62.5	0.18	0.91
	No	12	40.0	6	35.3	3	33.3	21	37.5		
Altered Sensorium	Yes	9	30.0	10	58.8	1	11.1	20	35.7	6.74	0.034*, S
	No	21	70.0	7	41.2	8	88.9	36	64.3		
Chi-square test											
* P < 0.05, Sig.											
Clinical Features Amongst Patients with Hyponatremia											
Associated Morbidities Among Stroke Patients with Hyponatremia (N = 56)											
Co-Morbidities		**SIADH (N = 30)**		**CSWS (N = 17)**		**Others (N = 9)**		**Total**		**Significance**	
		No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**X^2**	**P**
Diabetes	Yes	16	53.3	9	52.9	5	55.6	30	53.6	0.02	0.99
	No	14	46.7	8	47.1	4	44.4	26	46.4		
Hypertension	Yes	20	66.7	11	64.7	7	77.8	38	67.9	0.5	0.78
	No	10	33.3	6	35.3	2	22.2	18	32.1		
IHD	Yes	6	20.0	3	17.6	1	11.1	10	17.9	0.37	0.83
	No	24	80.0	14	82.4	8	88.9	46	82.1		
BA/COPD	Yes	1	3.3	0	0.0	0	0.0	1	1.8	0.88	0.64
	No	26	86.7	16	94.1	9	100.0	51	91.1		
Chi-square test											
P > 0.05, Not Sig.											
Comorbidities Amongst Patients with SIADH and CSWS											
Table 3											

Major clinical features were tabulated and compared between SIADH and CSWS; it was observed that a statistically significant (p = 0.034) number of patients in the CSWS group (64.7% and 58.8%) had headache and altered sensorium, respectively, which was more as compared to SIADH.

Comorbidities were compared amongst patients with SIADH and CSWS, and 53.3% of SIADH patients had diabetes mellitus, 66.7% hypertension, and 20% IHD, which were slightly more than those of CSWS.

Various Factors Amongst Stroke Patients with Hyponatremia (N = 56)						
Factor	**Category**	**SIADH**	**CSWS**	**Others**	**Total**	**Significance**

		(N = 30)		(N = 17)		(N = 9)		(N = 56)			
		No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**X^2**	**P**
Type of Stroke	Cardioembolic	7	23.3	4	29.4	5	55.6	17	30.4	6.1	0.64
	Haemorrhagic	1	3.3	3	11.8	0	0.0	3	5.4		
	Atheroembolic	5	16.7	2	11.8	1	11.1	8	14.3		
	Ischemic - Thrombotic	16	53.3	8	47.1	3	33.3	27	48.2		
Circulation Involved	Anterior	17	57.0	8	47.1	5	55.5	30	53.6		
	Posterior	10	33.3	8	47.1	3	33.3	21	37.5	1.05	0.9
	Watershed	3	10.0	1	5.9	1	11.1	5	8.9		
Chi-square test											
P > 0.05, Not Sig.											

Further Subtypes of Strokes in SIADH and CSWS

Table 4

Further classifying SIADH and CSWS patients based on stroke subtypes, it was observed that a significant number of patients (11.8%) of CSWS had hemorrhagic strokes than SIADH patients (3.3%). Thrombotic strokes dominated both groups.

Artery Affected	**SIADH (N)**	**CSWS (N)**	**Others (N)**
ACA	1	2	None
MCA	17	8	5
PCA	5	3	2
Classification as per the Vessel Involved			
Lab Parameter	**SIADH**	**CSWS**	**P-Value**
Serum Sodium (mEq/L)	131±2.5	129±1.6	0.1
Serum Uric Acid	4.1±0.92	5.6±0.72	0.02
Serum Osmolality	249±7.3	247±8.1	0.14
Urine Osmolality	1031±33	981±24	0.06
Urine Sodium	54±15.4	99±5.2	0.001
Student T-Test			
p value<0.05=significant			
Laboratory Parameters in Hyponatremia			

Table 5

Stroke patients with hyponatremia were classified as per the artery involved in stroke: PCA (Posterior Cerebral Artery), ACA (Anterior Cerebral) artery, and MCA (Middle Cerebral Artery). Patients with SIADH were found to have more strokes in the posterior circulation.

Major laboratory parameters were tabulated amongst patients with SIADH and CSWS, and it was observed that serum uric acid levels were lower (4.1±0.92) for SIADH as compared to CSWS, which was statistically significant (p = 0.02), and that urine sodium levels were higher (99±5.2) for CSWS patients than for SIADH, which was statistically significant (p = 0.001).

DISCUSSION

This study was conducted among newly diagnosed patients with acute stroke to delineate the cause of low sodium levels and to compare and contrast between SIADH and CSWS.

In our study, the incidence of hyponatremia was 56%, while in that done by Saleem et al., it was 35%.[6]

In our study, amongst the cases with hyponatremia, 53.57% patients had SIADH and 30.3% patients had CSWS, whereas in the study by Karunanandham S. et al. done on 202 stroke patients, 78 had hyponatremia, out of which 55.1% had SIADH and only 19.2% had CSWS.[7]

In another study conducted by Kalita J. et al. in Lucknow, India, where 100 stroke patients were studied, 7% of the patients with hyponatremia had SIADH, 44.2% had CSWS, and miscellaneous causes were 32.6%.[8]

As regards age, hyponatremia was seen to occur more in the elderly who presented with strokes (>65 years) in this study, which is comparable with other studies. No gender predilections were noted.

In this study, a larger number of patients with hyponatremia presented with headache (62.5%) and altered sensorium (64.3%), reflecting cortical involvement.

There was no significant difference in comorbidities in patients that had hyponatremia and those that did not.

Our study compared the clinical, radiological, and demographic factors between normonatremic and hyponatremic stroke patients at the outset, which was not done in other studies.

As regards the severity of stroke, it was observed in this study that the majority of the patients with hyponatremia (88%) had an NIHSS severity grading of moderate-severe to severe, emphasizing that hyponatremia is an important feature/marker of severe strokes.

When classified according to stroke subtypes, the majority of the strokes with or without hyponatremia were ischemic (93–95%), as is supported by other studies.

A slight preponderance (30%) of cardioembolic strokes was noted in the hyponatremia group. In the study conducted by Saleem S., 88% of patients with hyponatremia had strokes in the anterior circulation (MCA territory) than posterior (12%)[6], which is supported by our study.

Our study also included patients having watershed area infarcts, which were not included in other similar studies.

In our study, 53.5% of patients with hyponatremia had SIADH, 30.3% were found to have CSWS, and the rest, 16.07%, were categorized as others, where they did not fit the criteria of either SIADH or CSWS.

Clinical features between SIADH and CSWS were similar, except a statistically significant higher prevalence of altered sensorium ($p = 0.034$, 58.8%) in the CSWS group compared to the SIADH group, supporting its cortical origin.

Out of the 20 patients having CSWS, 17 patients had altered sensorium due to the hyponatremia per say, and 3 patients had altered sensorium due to cerebral edema, which was also evident in their CT/MRI images.

The comorbidities of the cases that had SIADH and CSWS were not significantly different from each other.

In our study, 97% of patients with SIADH had ischemic strokes, whereas only 3% had hemorrhagic stroke; whereas, looking into the study done by Saleem et al., 65% of SIADH cases had hemorrhagic strokes, with only 35% having ischemic strokes.[6]

In patients with CSWS, 88% had ischemic strokes**,** but 12% had hemorrhagic strokes, which is significantly larger as compared to those with SIADH**,** which was comparable to other studies.

Regarding the severity of stroke, the majority of the patients with CSWS (58.8%) graded severe (scores 21–42) on the NIHSS stroke scale, as compared to moderate-severe (scores 16–20) with SIADH.

The distribution of strokes was similar between both groups, with strokes in the anterior circulation (MCA territory) predominating (54%), more than posterior (37.5%), and then watershed infarcts (9%).

The main laboratory characteristics of SIADH and CSWS were tabulated, and in support of other similar studies, the serum uric acid levels were lower for the SIADH group (4.1± 0.92) than for CSWS (5.6± 0.72) as per the criteria, which was statistically significant ($p < 0.05$).

Both SIADH and CSWS had high values of urine specific gravity and urine osmolality. Both diseases had higher urinary excretion of sodium, but it was higher in CSWS than in SIADH, which is supported by other studies, and was statistically significant ($p<0.05$).

The mean sodium levels in the hyponatremia group were 131.8 ±3.6 mEq/L, with 119 being the lowest value and 135 being the upper limit.

Considering the severity of hyponatremia graded by the European Society Guidelines, the majority of the patients had mild hyponatremia; however, a significant number (11%) of patients with CSWS had severe hyponatremia (<125 mEq/L) compared to only 3% with SIADH.

It has been reported that hyponatremia accounts for 3–35% of inpatients, while the incidence in neurological patients has been reported to be as high as 50%. It resulted in higher mortality, hospital costs, readmission rates, and longer hospital stay.[2]

Other than the above, certain infections, restriction of salt in the diet for hypertension control, and drugs like diuretics can all cause hyponatremia.

Differentiation between SIADH and CSWS is necessary as their management strategies differ significantly.

SIADH, causing hyponatremia, is treated mainly by restriction of fluids and by use of Vaptans, whereas CSWS is treated by replacement of fluids and adjunctive therapy like fludrocortisone.

Hence, before any treatment is started, the exact cause of low sodium levels has to be ascertained; and risk groups predisposing towards hyponatremia must be identified.

CONCLUSION

Elderly (>65 years of age) stroke patients are more likely to be susceptible to hyponatremia.

- Stroke patients who present with headache or altered sensorium are more likely to have hyponatremia.
- Patients with hemorrhagic stroke are more likely to have CSWS, as compared to SIADH.
- In the setting of true hyponatremia in stroke patients, a higher urinary sodium level and a normal-high uric acid level are likely to be CSWS.

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