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

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Abstract

Background— Hyponatremia, defined as a serum sodium level of ≤135 mmol/L, is a common electrolyte imbalance in neurological disorders such as stroke. It is predominantly caused by Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Cerebral Salt Wasting Syndrome (CSWS). This study investigates the clinical profile, incidence, and severity of hyponatremia in stroke patients, comparing SIADH and CSWS in a tertiary care hospital.

Methods— A descriptive cross-sectional study was conducted on 100 stroke patients admitted to Kasturba Hospital, Manipal, over 1.5 years. Patients were classified into hyponatremia (n=56) and non-hyponatremia (n=44) groups based on serum sodium levels. Detailed clinical examinations, radiological findings (CT, MRI), and laboratory parameters were assessed. Stroke severity was evaluated using the NIHSS scale, and causes of hyponatremia were categorized based on serum osmolality, urine sodium, and cortisol levels.

Results— Hyponatremia was observed in 56% of stroke patients. SIADH accounted for 53.35%, while 30% of cases were due to CSWS. Patients with CSWS exhibited more severe hyponatremia and higher stroke severity (58.8% classified as severe on the NIHSS scale) compared to those with SIADH (36.7%). Clinical features such as altered sensorium and headache were significantly more prevalent in the CSWS group. Stroke types were predominantly ischemic, with a higher incidence of hemorrhagic strokes in the CSWS group.

Conclusion— Hyponatremia is a common complication in stroke patients, with a higher prevalence in older individuals and those presenting with severe strokes. Differentiating between SIADH and CSWS is crucial, as their management differs significantly. Early diagnosis and appropriate treatment can reduce mortality and improve outcomes in stroke patients.

Keywords— Hyponatremia, Stroke, SIADH, CSWS, Electrolyte imbalance, NIHSS, Tertiary care hospital, India

INTRODUCTION

Stroke is defined as a sudden onset of focal neurological deficit 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 more when compared to western countries.[2] Hyponatremia means a serum sodium level of ≤135 mmol/L.[3] It is a frequently seen electrolyte abnormality in patients of neurological disorders such as stroke, meningitis, and subarachnoid hemorrhage, which is usually either due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting syndrome (CSWS).[4] Reports suggest that hyponatremia accounts for 3–35% of patients admitted in the hospital, while the incidence in neurological patients has been reported to be as high as 50% .[5] It results in higher mortality, hospital costs, and readmission rates, and longer hospital stay. 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. In SIADH, there is euvolemic hyponatremia, and there is a loss of the negative feedback system; thus, leading to an excess release of ADH from the posterior pituitary. Many central nervous system (CNS) diseases are associated with SIADH. Stroke, infection, trauma, hemorrhage, and psychosis all enhance ADH release .[6] The classic description of the CSWS includes that of excessive sodium excretion in the urine (natriuresis), and resultant water loss and dehydration. Therefore, it leads to low sodium levels and is seen to occur most commonly in patients of central nervous system diseases. In CSWS, there is a reduction in the blood volume. Due to the low sodium

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levels, there is a reduction in the effective osmolality of the plasma, to adapt to this change, water moves into the brain cells, leading to cerebral edema.[7] Hence, hyponatremia is an important established cause of mortality and future morbidity in cerebrovascular accidents (CVA). Timely treatment is highly 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 disorders of euvolemic hyponatremia like SIADH and CSWS (that has a low blood volume with low sodium levels) must be differentiated. This is also 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.

AIM

To determine the incidence, clinical profile, and etiology of hyponatremia in newly diagnosed patients of stroke (Cerebrovascular accident).

REVIEW

- 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
- To compare between SIADH and CSWS based on the above

MATERIALS AND METHODS

The study was a hospital based, single center, descriptive type of cross-sectional study done over 1.5 years from 1/1/2021 to 31/7/2022 at Kasturba Hospital, Manipal, a unit of Kasturba Medical College, Manipal, Manipal Academy of Higher Education (MAHE).

The Inclusion Criteria was.

1. Patients >18 years of age
2. 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 hours of stroke onset.
3. Patients who have not received any anti-cerebral edema measures (like diuretics, steroids, mannitol) before presenting to the hospital.

The Exclusion Criteria was.

1. Patients with recurrent stroke or residual paralysis
2. Patients with a history of head trauma
3. Patients with any coexisting infection, e.g.- bacterial pneumonia, pulmonary tuberculosis (TB) or evidence of central nervous system (CNS) infection – meningitis, encephalitis
4. Patients with renal failure or chronic kidney disease (CKD)
5. Patients with liver failure or chronic liver disease
6. Patients with congestive cardiac failure (CCF)
7. Patients with any malignancy e.g.- bronchogenic carcinoma, leukemias
8. Patients with a h/o any surgery within the last 3 months
9. Patients with a h/o gastroenteritis and diarrhea
10. Patients taking any drugs that cause hyponatremia e.g.- Diuretics, Carbamazepine, Fluoxetine
11. Patients with serum glucose >300 mg/dl or TG>400 mg/dl
12. H/o any monoclonal gammopathy/MDS/amyloidosis/ IVIG (intravenous immunoglobulin) therapy
13. Patients with any pre-existing thyroid disease

Statistical analysis

1. Results are presented as Mean, SD and range values for continuous data and frequencies as number & percentages.
2. Unpaired t-test was used to compare the means of two groups.
3. Categorical data was analyzed by Chi-square test.
4. A P value of 0.05 or less was considered for statistical significance. SPSS (Version 17, IBM) software was used for data analysis.
5. All the data was entered and tabulated in Microsoft Excel before analysis.
6. Descriptive statistics are given by frequency tables, percentages, graphs, and using mean and Standard Deviation wherever necessary.

- Definition of controls: Patients who fit the above inclusion criteria, with an initial laboratory serum sodium value in peripheral blood being >135 mEq/L were taken as controls.
- Definition of cases: Patients who fit the above inclusion criteria, with an initial laboratory serum sodium value in peripheral blood being <= 135 mEq/L were taken as cases.

Data Collection

1. For all patients that fit into 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 patients. Both cases and controls were taken from the time of admission from the OPD/Emergency until the initial investigations sent.
3. Complete physical examination, especially 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/Hemorrhagic stroke

6. NIHSS Stroke scale (National Institute of Health Stroke Scale) calculated for all these patients and severity of stroke graded as per the above scale.
7. Each stroke patient further classified into Anterior circulation/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 obtained. Serum osmolality <275 mOsm/Kg and a serum sodium <125 mEq/Liter 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 were sent to find out the etiology of hyponatremia.
10. Cause of hyponatremia classified into SIADH, CSWS, and other causes based on the results.
11. Institutional ethical committee clearance was received (IEC: 49/2021) and CTRI registration done before starting any recruitment.
12. The following parameters were recorded:
    a) Age and Gender
    b) Mode of presentation
    c) Comorbid conditions: Chronic obstructive pulmonary disease (COPD)/Bronchial asthma, Diabetes Mellitus, Ischemic Heart Disease, and Hypertension
    d) CT Scan and MRI reports and Angiographic reports regarding type of stroke and area/vessel involved.
    e) Biochemical parameters as mentioned above.

OBSERVATIONS AND RESULTS

1. There was a total of 100 (N) patients with stroke, out of which fifty-six were cases (56%) – patients with hyponatremia, and forty-four were controls (44%) – patients without hyponatremia (Table 1). Hence incidence of hyponatremia in the study population was 56%.
2. Age Distribution The average age of the patients without hyponatremia was 61±12 years, and 60±14 years in cases with hyponatremia (Table 1 and 2)
3. Gender distribution: It was observed that majority of the patients in the hyponatremia group (70%) were male, and 30% were female. Similar observations were made in the patients without hyponatremia – 71% were male and 29% were female (Table 4)
4. 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 (Table 5).
5. Major clinical features: In our study cohort, major clinical features were compared between the hyponatremia group and controls (Table 7); with 89% of the patients with hyponatremia having motor deficit, 91.1% having cranial nerve involvement, 35.7% altered sensorium, and 62.5% had headache (Figure 1). Patients with hyponatremia had a statistically significant (p=0.05) prevalence of headache as compared to controls.
6. Comorbidities: Our study showed that Diabetics were more (53.6%) in the hyponatremia group than the controls, whereas; prevalence of Hypertension (70.5%) and IHD (ischemic heart disease) (20.5%) was more in the control group (Table 8).
7. Classification of Stroke: Broad classification of strokes between the two groups revealed that in the no- hyponatremia group, 95.4% strokes were ischemic, and the rest 4.6% were hemorrhagic; while for the hyponatremia group, they were 93% and 7.1% respectively (Figures 2 and 3). The smaller number of hemorrhagic strokes in the study could be attributed towards the exclusion criteria.
8. Further subtypes of strokes: Cases with hyponatremia were further classified according to stroke subtypes; and it was seen that 48% had thrombotic strokes, 7.1% hemorrhagic, 1.8% were lacunar, and 30.4% were cardioembolic compared to 15% in the control group (Figure 4)
9. Severity of stroke: The severity of stroke was compared in both the groups as per the Severity on the NIHSS Stroke Scale as mentioned above. There were more percentage of Moderate-Severe (44.6%) and Severe (44.6%) strokes in the hyponatremia group as compared to the control group (Figure 5).
10. Circulation involved: When comparing the circulation involved between the two groups, patients with hyponatremia had 53.6% strokes in the anterior circulation, 37.5% posterior; and 8.9% watershed infarcts, which was more than the control group (2.3%). (Figure 6)
11. Etiology of hyponatremia: In our study, among the patients with hyponatremia (total N=56), 53.35% were found to have SIADH, 30% were found to have CSWS, and 16.07% did not fit into criteria for either, hence classified as Others (Figure 7).
12. Severity of hyponatremia: Patients with hyponatremia were classified based on Severity of the same by the European Society Guidelines as mentioned above. For patients with SIADH, Mild hyponatremia was seen in 80%, 16.7% with Moderate, and 3.3% patients with Severe; and the same for CSWS patients was 70.6%, 17.6% and 11.8% (which was more than that for SIADH) respectively (Figure 8).
13. Clinical features amongst patients with hyponatremia: Major clinical features were tabulated (Table 9) 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.
14. Comorbidities amongst patients with hyponatremia: Comorbidities were compared amongst patients with SIADH and CSWS, and 53.3% of SIADH patients

TABLE 1: Incidence of Hyponatremia and distribution of patients.

STUDY SUBJECTS	
Total no. of patients with stroke (n)	100
With Hyponatremia (Sodium level ≤ 135	56
Without Hyponatremia (Sodium level >135	44

TABLE 2: Mean age of the patients.

No Hyponatremia (n=44)		Hyponatremia (n=56)		Total (n=100)	
Mean Age	SD	Mean Age	SD	Mean	SD
61.1	12.4	60.9	14.9	61.0	13.8
19 - 89 yrs.		28 - 92 yrs.		19 - 92 yrs.	

TABLE 3: Age distribution of the patients.

Age (Yrs)	No Hyponatremia (n=44)		Hyponatremia (n=56)		Total (n=100)
	No.	%	No.	%	No.
< 30	1	2.3	1	1.8	2
31-40	1	2.3	6	10.7	7
41-50	4	9.1	7	12.5	11
51-60	17	38.6	10	17.9	27
61-70	12	27.3	18	32.1	30
71-80	7	15.9	10	17.9	17
> 80	2	4.5	4	7.1	6
Total	44	100.0	56	100.0	100
$X^2 = 7.27$, P = 0.30, NS					

TABLE 4: Gender distribution amongst the patients.

Gender	No Hyponatremia (n=44)		Hyponatremia (n=56)		Total (n=100)
	No.	%	No.	%	No.
Male	31	70.5	39	69.6	70
Female	13	29.5	17	30.4	30
Total	44	100.0	56	100.0	100
$X^2 = 0.01$, P = 0.93, NS					

TABLE 5: Sodium level in patients with hyponatremia.

	Hyponatremia (n=56)	Significance
Mean	131.8	
SD	3.6	t = 11.45, P < 0.001, HS
Range	119 - 135	
t: Unpaired t test		
* P < 0.001, High Sig.		

TABLE 6: Sodium level in patients without hyponatremia.

	No Hyponatremia (n=44)	Significance
Mean	138.8	
SD	2.1	t = 12.55, P < 0.001, HS
Range	136 - 144	
t: Unpaired t test		
* P < 0.001, High Sig.		

TABLE 7: Motor involvement compared between the hyponatremia and control groups.

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						

TABLE 8: Associated co-morbid conditions assessed between the hyponatremia group and control group.

Comorbidities		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.

TABLE 9: 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	0.0348*
	No	21	70.0	7	41.2	8	88.9	36	64.3		

Chi-square test

* P < 0.05, Sig.

TABLE 10: Associated morbidities 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
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, Sig.

TABLE 11: Various factors amongst stroke patients with hyponatremia (n = 56)

Factor	Category	SIADH (n=30)		CSWS (n=17)		Others (n=9)		Total (N=56)		Significance	
		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	1.05	0.9
	Posterior	10	33.3	8	47.1	3	33.3	21	37.5		
	Watershed	3	10.0	1	5.9	1	11.1	5	8.9		

Chi-square test

* P < 0.05, Sig.

TABLE 12: Artery affected in relation to cause of hyponatremia.

Artery Affected	SIADH (n)	CSWS (n)	Others (n)
ACA	1	2	None
MCA	17	8	5
PCA	5	3	2

TABLE 13: Laboratory parameters in hyponatremia.

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			

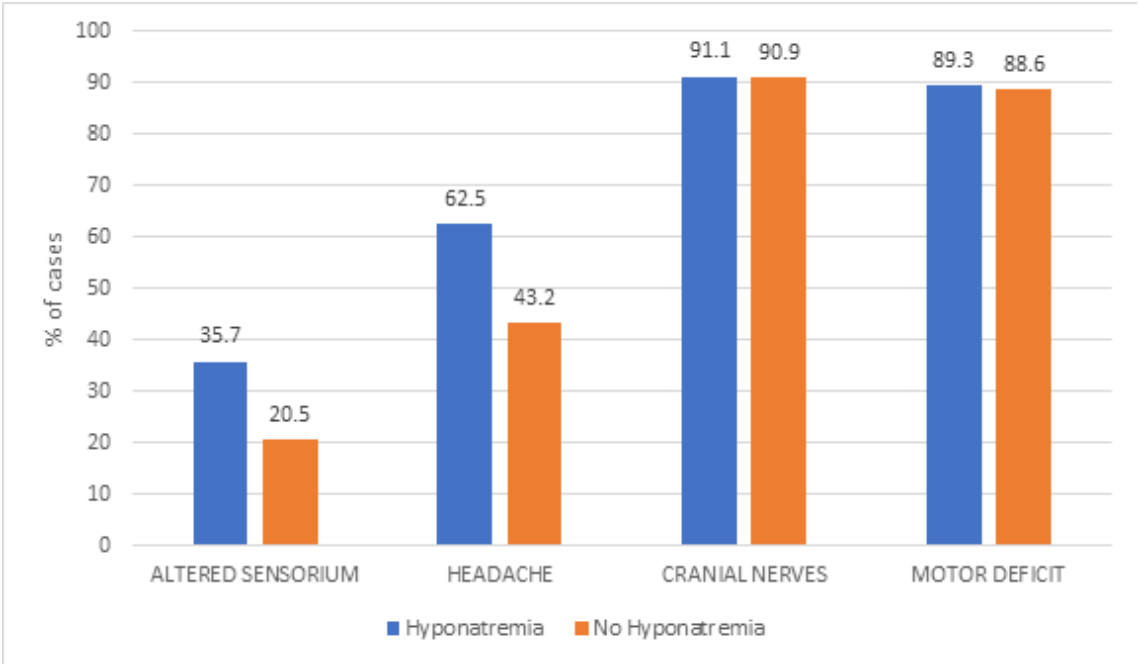


FIGURE 1: Bar graph showing major clinical features in the two groups.

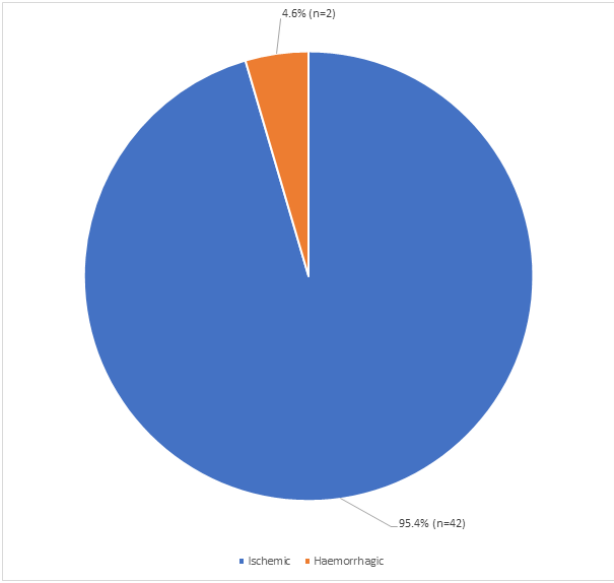


FIGURE 2: No Hyponatremia

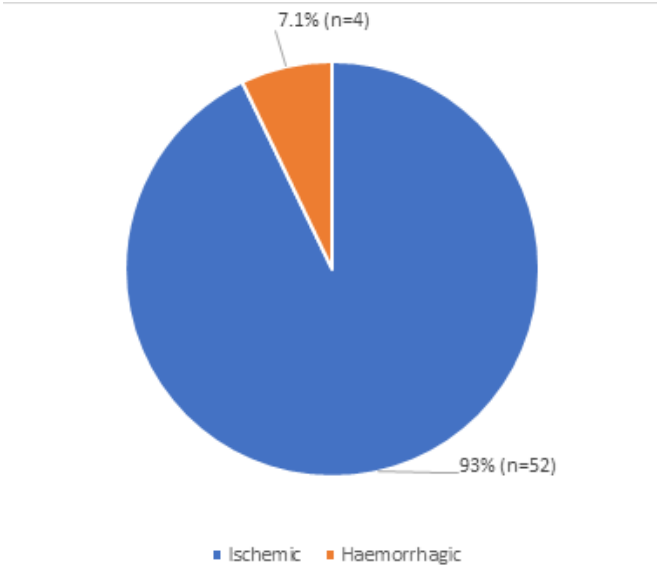


FIGURE 3: Hyponatremia

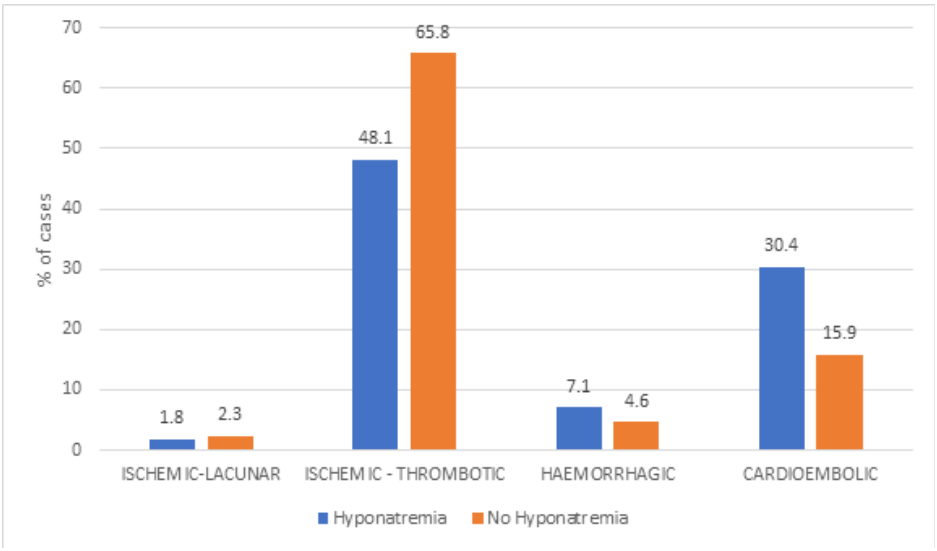


FIGURE 4: Stroke Sub-types.

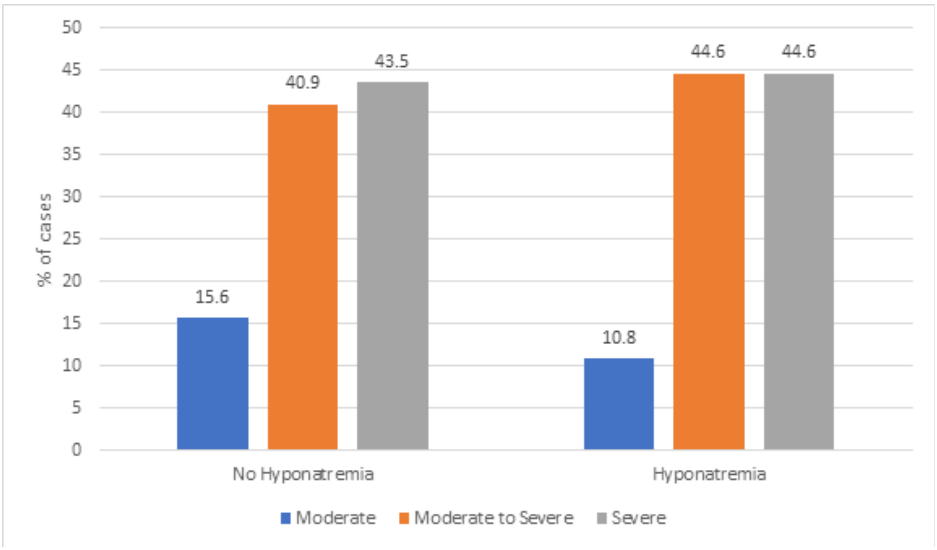


FIGURE 5: NIHSS Stroke Scale Severity

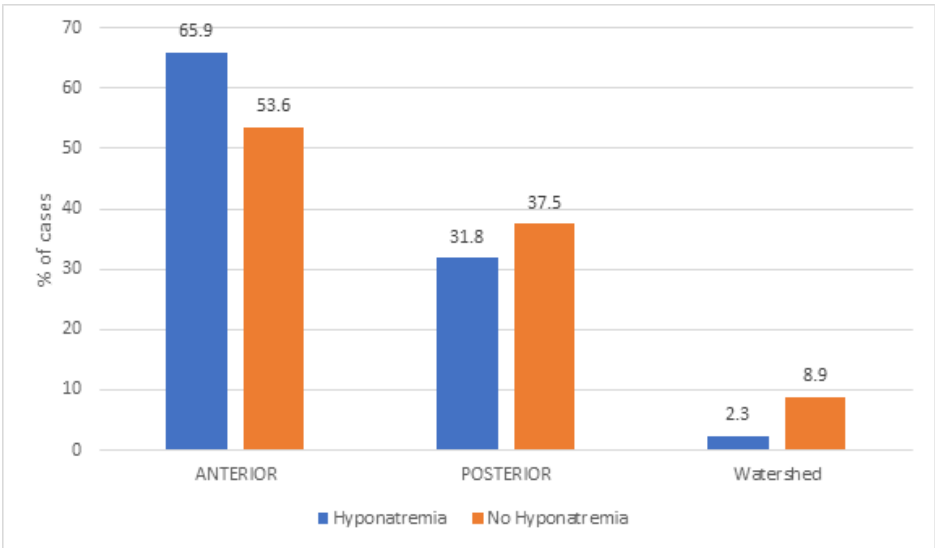


FIGURE 6: Circulation involved

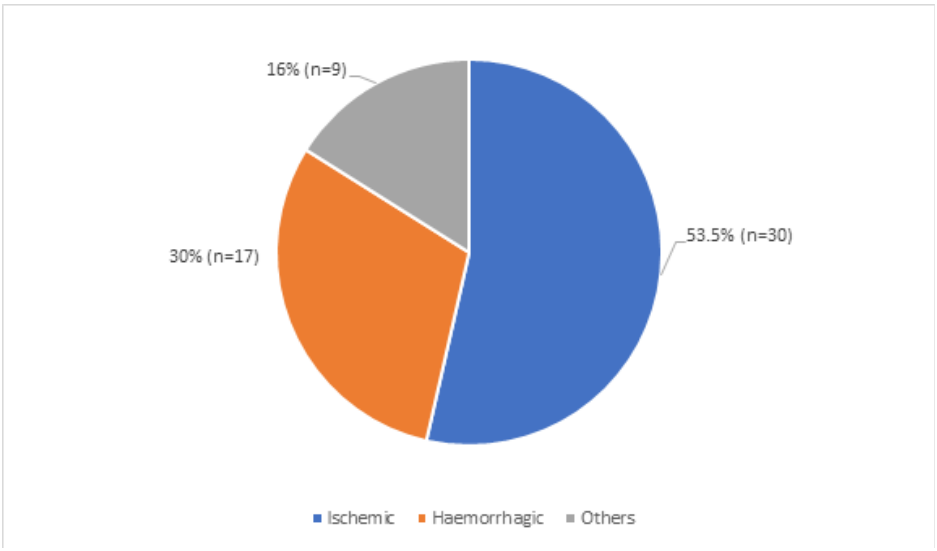


FIGURE 7: Cause of Hyponatremia.

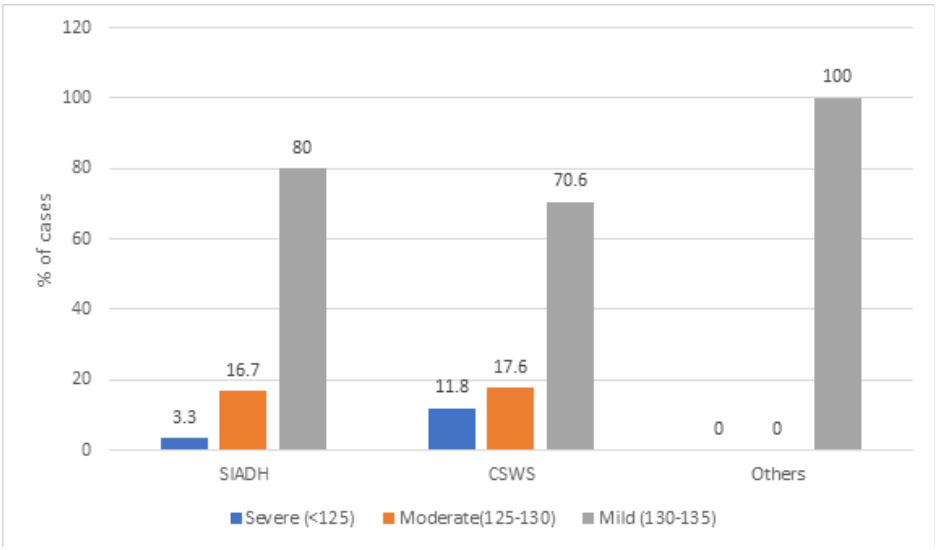


FIGURE 5: Severity of Hyponatremia

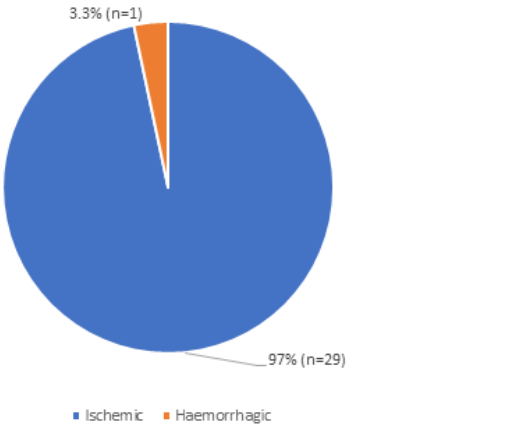


FIGURE 9: Severity of Hyponatremia Type of Stroke in SIADH.

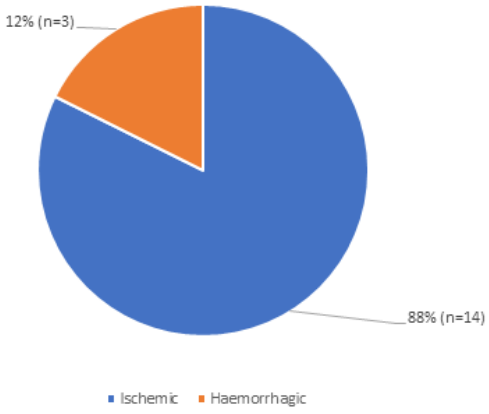


FIGURE 10: Type of Stroke in CSWS

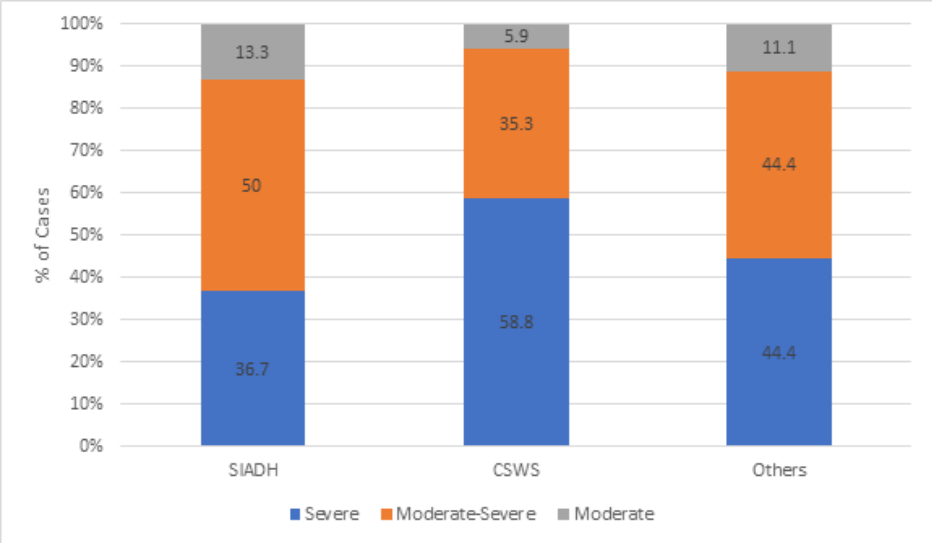


FIGURE 11: NIHSS SCALE SEVERITY

1. had Diabetes mellitus, 66.7% Hypertension, 20% IHD, which were slightly more than that of CSWS respectively (Table 10)
2. Type of stroke in patients with hyponatremia: When classified according to the type of stroke, 97% of patients with SIADH had Ischemic stroke, and only 3% had hemorrhagic stroke; whereas the same was 88% and 12% respectively for CSWS patients (they had a greater number of hemorrhagic strokes as compared to SIADH) (Figure 9 and 10).
3. Further stroke subtypes: Further classifying SIADH and CSWS patients based on stroke subtypes, it was observed that a considerable number of patients (11.8%) of CSWS had hemorrhagic strokes than SIADH patients (3.3%). Thrombotic strokes dominated both groups (Table 11).
4. Severity of stroke amongst patients with hyponatremia: Severity of strokes was calculated for both SIADH and CSWS patients as per the severity on the NIHSS Stroke Scale as mentioned above; and it was observed that a considerable number of patients with CSWS (58.8%) had Severe strokes as compared to 36.7% patients in SIADH (Figure 11).
5. Classification based on circulation: Stroke patients with hyponatremia were classified as per the artery involved in stroke – Posterior Cerebral Artery (PCA), Anterior Cerebral (ACA) artery and the Middle Cerebral Artery (MCA) (Table 12). Patients with SIADH were found to have more strokes in the posterior circulation.
6. Laboratory parameters: 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) (Table 13).

DISCUSSION

A. This study was conducted in 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%.[8] 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; seventy-eight had hyponatremia, out of which 55.1 % had SIADH and only 19.2% % had CSWS.[9] In another study conducted by Kalita J et al in Lucknow, India; where one hundred stroke patients were studied, 7% of the patients with hyponatremia had SIADH, 44.2% had CSWS; and miscellaneous causes were 32.6%.[10] As regards to 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.

B. 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 demographical 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 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.

C. When classified according to stroke subtypes, 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 noted in the hyponatremia group. In the study conducted by Saleem S, 88% of patients with hyponatremia had strokes in the anterior circulation

TABLE 20: Comparison of hyponatremia and mortality.[1]

Study	Design	Sample	Definition of hyponatremia	Prevalence of hyponatremia, %	Associations of hyponatremia
Ischemic stroke Fofiet al. [4],2012	Prospective	n = 475; 53.9% male; mean age 67.0 years	Na<136 mmol/L	6.3	Increased in-hospital mortality
Huang et al. [5], 2012	Prospective	n = 925; 52.5% male; mean age 69.5 years	Na<135 mmol/L	11.6	Higher 3-year mortality (but not short-term mortality within 3 months)
Rodrigues et al. [6], 2014	Retrospective	n = 3,585; 49.6% male; mean age 71.0 years	Na<135 mmol/L	16.0	Higher admission NIHSS values, lower admission mBI values, worse disposition at discharge from hospital, and higher 3- and 12-month mortality
Lasek-Bal et al. [7], 2014	Prospective	n = 464; 46.1% male; mean age 70.4 years	Na<136 mmol/L	18.9	Higher mortality within 1 month, more severe neurological patients' state in both the acute and subacute phases of stroke
Beiet al. [8], 2017	Prospective	n = 3,314; 57.7% male; mean age 68.6 years	Na<135 mmol/L	3.9	Higher admission mRS and NIHSS scores No association with in-hospital mortality
Gaoet al. [9], 2018	Retrospective	n = 718; 21.4% male; median age 73 years	Na<135 mmol/L	15.2	Association with 1-month mortality only in univariate analysis
Acute ischemic or hemorrhagic stroke Soiza et al [10],2015	Retrospective	n = 8,540; 47.4% male; mean age 77.3 years	Na<135 mmol/L	13.8	Higher mortality (within 1 week - 11 years) in patients <75 years
Hemorrhagic stroke Kuramatsu et al. [11],2014	Retrospective	n = 464; 45.0% male; mean age 69.6 years	Na<135 mmol/L	15.6	Increased in-hospital mortality and within 90 days of index stroke; higher admission NIHSS values; lower Glasgow Coma Scale
Gray et al. [12], 2014	Retrospective	n = 99; 61.6% males; mean age 58 years	Na<135 mmol/L	24	Increased in-hospital complications (fever, infection and a longer hospitalization); no association with in-hospital mortality
Carcel et al. [13], 2016	Retrospective analysis of a randomized trial	n = 3,002; 62.8% males; 64±13 years	Na<135 mmol/L	12	Increased mortality within 3 months; larger baseline intracerebral hemorrhage volume

NIHSS, National Institutes of Health Stroke Scale; mBI, modified Barthel Index; mRS, modified Rankin Scale.

(MCA territory) than posterior (12%),[8] which is supported by our study. Our study also included patients having Watershed area infarcts, which were not included in other similar studies.

D. In our study, 53.5% of patients with hyponatremia had SIADH, 30.3% were found to have CSWS, and rest 16.07% 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 twenty patients having CSWS, seventeen patients had altered sensorium due to the hyponatremia per say, and three 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.

E. 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% SIADH cases had hemorrhagic strokes, with only 35% having ischemic stroke.[8] In patients with CSWS, 88% had ischemic stroke, but 12% had hemorrhagic strokes, which is significantly larger as compared to those with SIADH, which is comparable to other studies.

F. Regarding the severity of stroke, 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. 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%).

G. 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, to 135 being the upper limit. Considering the severity of hyponatremia graded by the European Society Guidelines, majority of the patients had mild hyponatremia; however, a considerable number (11%) of patients of CSWS had severe hyponatremia (<125 mEq/L) compared to only 3% with SIADH.

H. 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, and 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, all can cause hyponatremia. Differentiation between SIADH and CSWS is necessary as their management strategies differ significantly. SIADH causing hyponatremia is treated 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 must be ascertained; and risk groups predisposing towards hyponatremia must be identified.

CONCLUSION

The results of our study can be summarized as follows:

- 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 is likely to be CSWS.

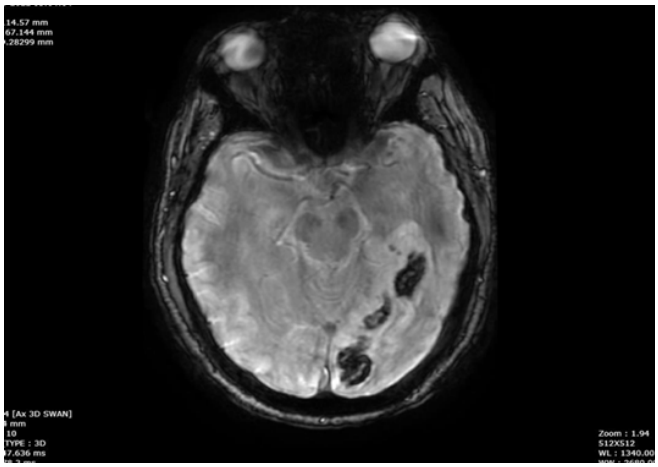
STRENGTHS AND LIMITATIONS

1. The strength of this study is that it compares the clinical, radiological, and demographical factors between normonatremic and hyponatremic stroke patients at the outset.
2. Limitations were of a Single Centre study, limited sample size, and that correlation of hyponatremia as a mortality indicator was not considered.
3. Patients with Minor Strokes (NIHSS scores 1-4) may not have presented to our tertiary care center.

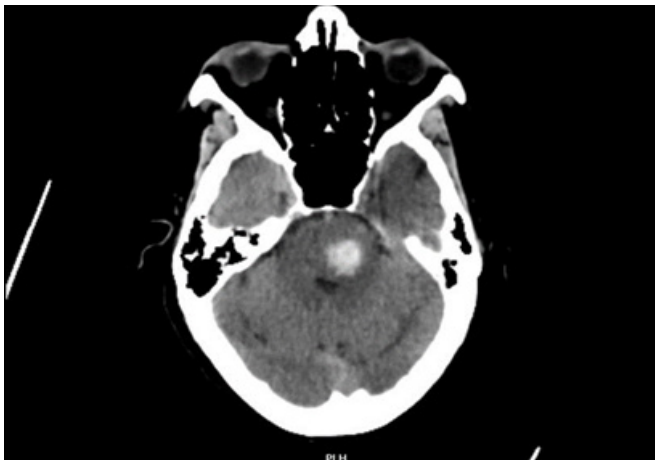
ANNEXURES:

IMAGES:

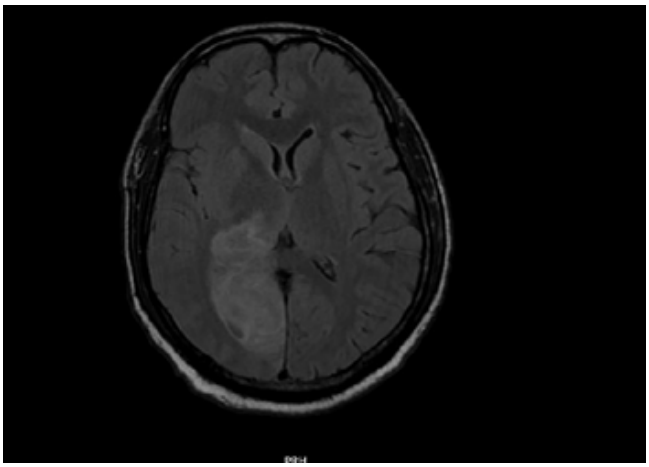
Select radiographic images of CT scans, MRI and CT Angiographies of the recruited patients are presented below.



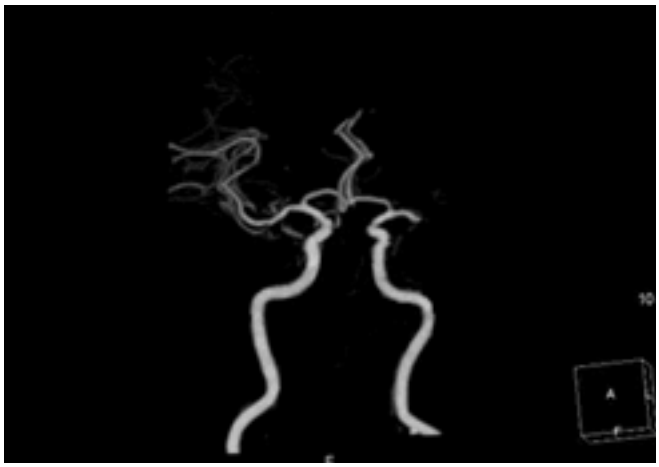
1: Case of Mr. ABC with MRI showing an acute infarct with hemorrhagic transformation in the left PCA territory.



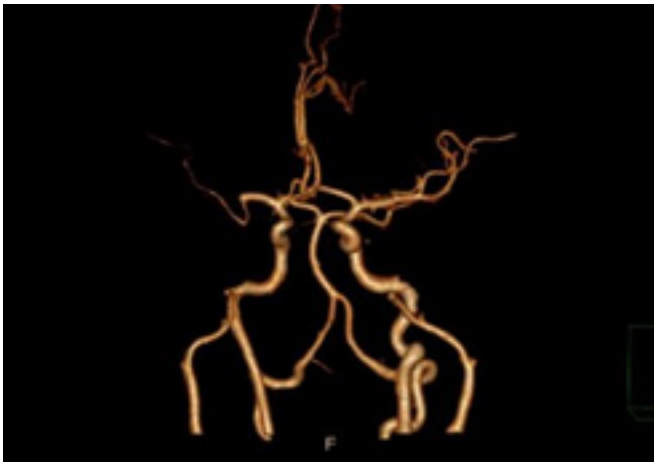
2: CT scan of a patient Mrs. DEF, showing acute intraparenchymal hemorrhage in the left pons.



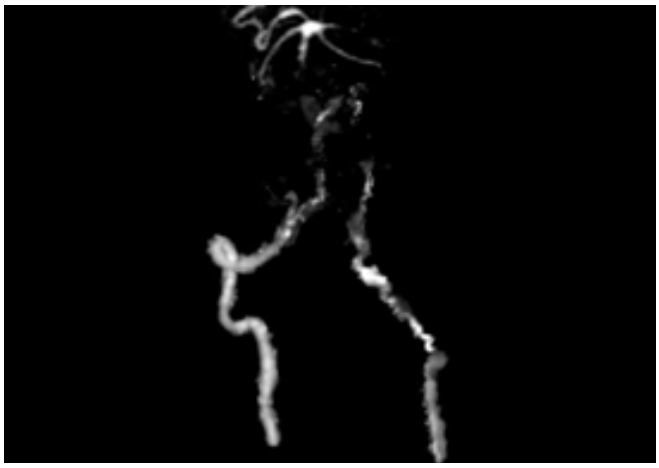
3: MRI of a 40-year-old male patient Mr. GHI, with FLAIR sequence showing an acute infarct in the right MCA territory with hemorrhagic transformation causing ipsilateral lateral ventricle compression with midline shift to the left.



4: CT angiography of a patient Mr. JKL with a left MCA territory infarct, showing M2, M3, M4 segment thrombosis/occlusion.



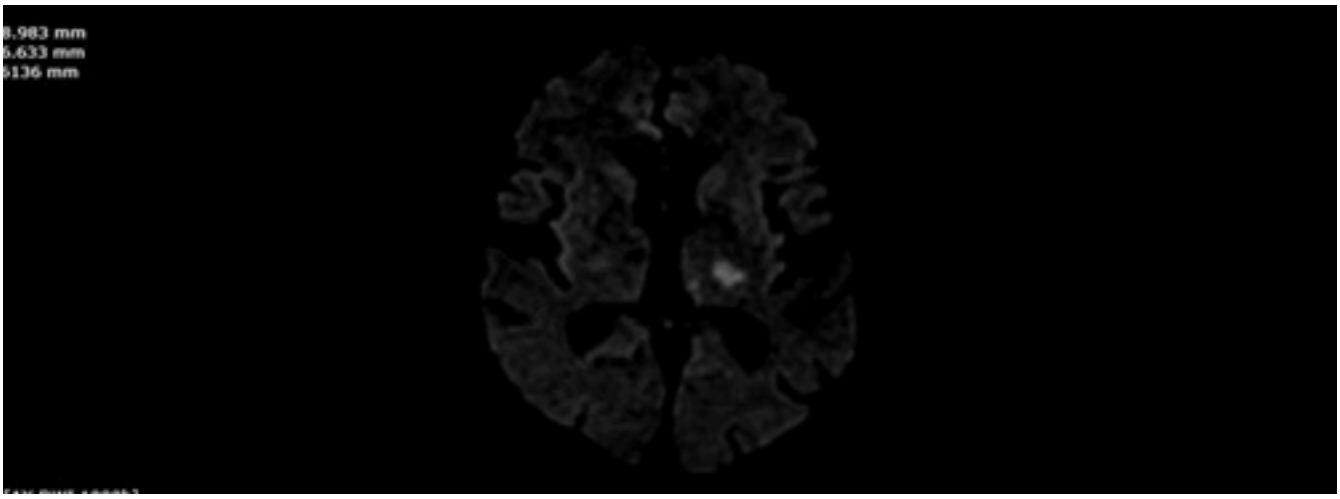
5: CT Angiography of a patient Mr. MNO, showing right MCA narrowing/occlusion and right ACA occlusion with extensive collateral formation.



6: CT Angiography of a patient Mr. PQR, showing occlusion/thrombosis of the Basilar artery and a few collaterals.

ANNEXURES (Continued):

IMAGES:
Select radiographic images of CT scans, MRI and CT Angiographies of the recruited patients are presented below.



7: Patient, Mrs. STU; a case of cerebrovascular accident with MRI showing an acute infarct in the left thalamus and left internal capsule (Left MCA territory).

REFERENCES

1. Liamis G, Barkas F, Megapanou E, et al. Hyponatremia in Acute Stroke Patients: Pathophysiology, Clinical Significance, and Management Options. Eur Neurol 2019;82(1–3):32–40.
2. Banerjee TK, Das SK. Fifty years of stroke researches in India. Ann Indian Acad Neurol 2016;19(1):1–8.
3. Adrogué HJ, Madias NE. The challenge of hyponatremia. J Am Soc Nephrol 2012;23(7):1140–8.
4. Alam MN, Uddin MJ, Rahman KM, et al. Electrolyte changes in stroke. Mymensingh Med J 2012;21(4):594–9.
5. Tisdall M, Crocker M, Watkiss J, Smith M. Disturbances of sodium in critically ill adult neurologic patients: a clinical review. J Neurosurg Anesthesiol 2006;18(1):57–63.
6. Boone M, Deen PMT. Physiology and pathophysiology of the vasopressin-regulated renal water reabsorption. Pflugers Arch 2008;456(6):1005–24.
7. Momi J, Tang CM, Abcar AC, Kujubu DA, Sim JJ. Hyponatremia—What Is Cerebral Salt Wasting? The Permanente Journal 2010;14(2):62–5.
8. Saleem S, Yousuf I, Gul A, Gupta S, Verma S. Hyponatremia in stroke. Ann Indian Acad Neurol 2014;17(1):55–7.
9. Karunanandham S, Rajappa T, Selvaraju K. Hyponatremia in Patients Admitted with Stroke. J Clin of Diagn Res.2018; 12(8):OC34-OC36.
10. Kalita J, Singh RK, Misra UK. Cerebral Salt Wasting Is the Most Common Cause of Hyponatremia in Stroke. J Stroke Cerebrovasc Dis 2017;26(5):1026–32.