http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i1.63

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Research Paper

Hyponatremia in Stroke: Cerebral Salt Wasting Versus Syndrome of Inappropriate Anti-Diuretic Hormone Secretion

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Abstract

Hyponatremia is the most common electrolyte abnormality seen in hospitalised patients and is also the most common electrolyte imbalance seen in critically ill neurologic patients. It can significantly alter the morbidity, short and long term mortality of the underlying disease.

The causes of hyponatremia are varied, but in neurologically ill patients, are most commonly attributed to Syndrome of Inappropriate Anti-diuresis and Cerebral Salt Wasting. Both these entities are cerebral in origin but have distinct pathophysiology, prognosis and treatment options.

In stroke SIADH (euvolemichyponatremia) occurs due to AVP secretion inappropriate to the osmotic threshold. The suppressed proximal renal tubular transport in this condition can lead on to bicarbonaturia and hypouricemia. The effective treatment is fluid restriction. Hypertonic saline therapy is reserved for cases of severe hyponatremia.

CSW, on the other hand, is essentially a volume depleted state, which occurs due to the combined effects of decreased sympathetic outflow and increased natriuretic peptides. This resultant natriuresis leads to volume depletion and an appropriate AVP response. So the treatment for CSW includes an aggressive volume replacement regimen with isotonic saline or in severe cases, hypertonic saline.

Thus most CSW patients meet the criteria for SIADH and have elevated AVP levels but worsen with the treatment protocol given for SIADH. This observation lead to the description of CSW as a separate entity and widespread studies were carried out to distinguish the two entities.

Hyponatremia, especially Cerebral Salt Wasting, occurring in the setting of stroke has been shown to worsen the prognosis of stroke, increase morbidity, short and long term mortality, and cause a poorer discharge disposition.

Aims and Objectives

- To study the prevalence of hyponatremia in the setting of acute stroke
- To distinguish between SIADH and CSW among hyponatremic patients
- To study the implication of SIADH and CSW on the short term outcome of stroke.

Materials and Methods

(i) **Source of Data:** Data consists of primary data collected by the principal investigator directly

from the patients who are admitted in the Government Medical College and Hospital

(ii) **Study Area:** Medical College hospital trichy

(iii) **Design of Study:** Cross sectional study

(iv) **Period of Study:** One year

(v) **Sample Size:** 50

Inclusion Criteria

Confirmed cases of stroke by history, neurologic and imaging modalities.

EXCLUSION CRITERIA

- Head injury
- CNS tumor
- Pulmonary tuberculosis
- Bacterial pneumonia
- Bronchogenic carcinoma
- Hematologic malignancies
- Recent surgery
- Meningitis
- Encephalitis
- Drug usage- SSRI, TCA, narcotics, NSAIDs, Antipsychotics, Carbamazepine, Cyclophosphamide, clofibrate, chlorpropamide.

The diagnosis was confirmed by imaging- CT scan or MRI. The stroke type- ischemic or hemorrhagic, the side of the stroke and the involved vascular territory was confirmed using the imaging study.

After ruling out the exclusion criteria, serial serum sodium levels were done. In patients with hyponatremia, plasma osmolality was measured to differentiate between true and pseudo-hyponatremia. Cerebral causes of hyponatremia were identified and classified as SIADH/CSW and treated as per the standard protocol. The patient was put on in-patient follow-up till discharge/ death. The patients with prior/ admission diuretic usage are not taken into the study group as cases.

Results

Table 1: Association of Demographic Variables & Clinical Variables with Hyponatremia

Clinical Variables	HYPONATREMIA				Sig
	Without [n=37]	SIADH [n=6]	CSW [n=4]	Others[n=3]	
AGE					
21 -40	5	0	0	0	
%	14%	0%	0%	0%	
41 – 60	21	2	0	0	
%	57%	33%	0%	0%	<0.05
61 – 80	7	4	3	3	
%	19%	67%	75%	100%	
>80	4	0	1	0	
%	11%	0%	25%	0%	
GENDER					
Male	30	4	3	1	
%	81%	67%	75%	33%	
Female	7	2	1	2	
%	19%	33%	25%	67%	>0.05
Types of Stroke					
Ischemic	30	5	2	3	
%	81.10%	83.30%	50.00%	100.00 %	
Hemorrhagic	7	1	0	0	
%	18.90%	16.70%	0.00%	0.00%	<0.001
Ischemic+Hemorrhagic	0	0	2	0	
%	0.00%	0.00%	50.00%	0.00%	
TERRITORY					
ACA	4	0	0	0	
%	10.80%	0.00%	0.00%	0.00%	
MCA	20	2	3	3	
%	54.10%	33.30%	75.00%	100.00 %	>0.05
PCA	13	4	1	0	
%	35.10%	66.70%	25.00%	0.00%	
SIDE					
RIGHT	20	4	3	0	
%	54.10%	66.70%	75.00%	0.00%	
LEFT	12	1	0	1	
%	32.40%	16.70%	0.00%	33.30%	>0.05
BILATERAL	5	1	1	2	
%	13.50%	16.70%	25.00%	66.70%	

Table 2: Association of Bio Chemical Properties with Hyponatremia

BIO CHEMICAL PROPERTIES				
Climinal Variables	HYPONATREMIA			
	SIADH [n=6]	CSW [n=4]	Others[n=3]	Sig
Volume Status				
Increased	3	0	0	
%	50.00%	0.00%	0.00%	
Decreased	0	4	0	
%	0.00%	100.00%	0.00%	<0.05
Normal	3	0	0	
%	50.00%	0.00%	0.00%	
Uric Acid -day5				
Decreased	0	3	0	
%	0.00%	75.00%	0.00%	<0.05
Normal	5	0	0	
%	100.00%	0.00%	0.00%	
1BUN/ Creatinine				
Increased	0	4	1	
%	0.00%	100.00%	33.30%	
Decreased	5	0	0	
%	100.00%	0.00%	0.00%	<0.05
Normal	0	0	1	
%	0.00%	0.00%	33.30%	
HCT Day5				
Increased	0	2	0	
%	0.00%	50.00%	0.00%	
Decreased	2	0	0	
%	33.30%	0.00%	0.00%	<0.05
Normal	4	1	0	
%	66.70%	25.00%	0.00%	
Albumin Day 5				
Decreased	1	0	0	
%	16.70%	0.00%	0.00%	<0.05
Normal	5	3	0	
%	83.30%	75.00%	0.00%	
Urine Sodium				
Increased	6	4	1	
%	100.00%	100.00%	33.33%	
Decreased	0	0	2	
%	0.00%	0.00%	66.67%	<0.05

Table 3: Age Distribution in Stroke and Hyponatremia

	HYPONATREMIA			
AGE	WITH	WITHOUT	TOTAL	(%)
21-40	0	5	5	10%
41 - 60	2	21	23	46%
61 - 80	7	10	17	34%
>80	1	4	5	10%
TOTAL	10	40	50	

Table 4: Age Distribution of SIADH and CSW

	Hyponatremia				
Age	SI ADH	CSW	Others	TOTAL	(%)
41 - 60	2	0	0	2	15%
61 - 80	4	3	3	10	77%
>80	0	1	0	1	23%
Total	6	4	3	13	

Table 5: Stroke Type in Hyponatre MIA

	Hyponatremia				
Stroke Type	SIADH	CSW	Others	TOTAL	(%)
Ischemic	5	2	3	10	77%
Hemorrhagic	1	0	0	1	8%
SAH	0	2	0	2	23%
Total	6	4	3	13	

Table 6: Treatment Outcome of SIADH vs CSW

	HYPONATREMIA					
Out Come	Without [n=37]	SIADH [n=6]	CSW [n=4]	Others[n=3]	T otal	
Cure	32	5	1	2	40	
Death	5	1	3	1	10	
Total	37	6	4	3	50	

Discussion

Stroke

In our study we analysed 50 patients with acute stroke to study the occurrence of hyponatremia. The majority of stroke patients, about 46%, belonged to the middle age i.e., 40 – 60 years of age. The mean age of stroke occurrence in males was 56.2 (± 14.5) and that of the females was 66.9 (± 17.3). This is comparable to the population based study by Dalal et al[42] in Mumbai where the mean age for stroke was 66 years, and in Trivandrum by Sridharan et al[43] where the mean age was 67 years.

The majority of males belonged to 40-60 years age group. The prevalence of stroke in females, however was higher in the 60 to 80 year age group. Thus a higher age stratified prevalence for females was found, which is comparable to the data from the 2008 Mumbai stroke registry[42] where a mean of 63.4 years was recorded for females. Of the stroke patients in our study group, 76% were male and 24% were female .The prevalence of ischemic stroke was higher (80%), of which 6 patients had lacunar stroke, 5 patients had a massive infarct.

Hemorrhagic stroke was seen in 20%, with 16% having intracerebral bleed and 4% having sub-arachnoid haemorrhage. This is comparable to the Mumbai stroke registry[42], where 80% of strokes were attributed to be ischemia and 17.7% to haemorrhage. Accelerated hypertension was the cause of haemorrhage in 4 patients with intra cerebral bleed. 52% had stroke corresponding to the Middle Cerebral Artery territory, 40% with Posterior cerebral artery involvement and 8% with Anterior Cerebral circulation involvement.

Hyponatremia

The prevalence of hyponatremia due to cerebral causes was noted in 20% of the acute stroke patients. The prevalence is slightly higher than the study by Kuramatsu et al[44] where prevalence was 15%. Rodrigues B[43] reported a prevalence of 16% and Soiza et al[45] 13.8%.

Of the hyponatremic patients, there was a higher prevalence of SIADH (46%). CSW contributed to 31%. The study by Saleem et al[15] showed the respective prevalences to be 67% and 33% .The prevalence of hyponatremia was the most in the 61-80 year age group (70%). The prevalence was lower among other age groups and this reached statistical significance ($p<0.05$). 67% of the patients who developed SIADH were of the 61-80 years age group.

All the patients who developed Cerebral Salt Wasting on the other hand belonged to a higher

age group (> 65 years). ($p<0.05$) .The trend of hyponatremia prevalence was more in males (70%) but did not reach statistical significance ($p>0.05$) .Both SIADH and CSW showed a higher male prevalence, 67% and 75% respectively. All the subarachnoid haemorrhage patients in our study developed hyponatremia. Out of the Ischemic stroke patients 18% had hyponatremia. Hyponatremia was seen in 13% of patients with intracerebral haemorrhage. The most common stroke type seen in hyponatremic patients was ischemic stroke (77%)

Among SIADH patients, 83% had ischemic stroke and 17% had intra cerebral hemorrhage. Saleem et al[15] in his study, showed 35% and 65% respectively. Among cerebral salt wasting patients, ischemic stroke was found in 50% of patients and SAH was found in 50% patients. In the study by Saleem et al 33% and 67% were the prevalence.[15]

Of the hyponatremia patients, 50% of patients had Middle cerebral territory and 50% had posterior cerebral artery territory involvement. None of our patients with ACA territory stroke developed hyponatremia. The majority of patients with SIADH had a posterior circulation stroke, 67%, and 33% had Middle Cerebral Territory stroke. Saleem et al[15] however, reported 13% and 86% respectively

In CSW, 75% had Middle Cerebral Artery territory involvement and 25% had posterior circulation stroke. This was comparable with Saleem et al's study (15%) who reported 85% and 15% respectively. The mean duration of hospital stay was significantly different in patients with hyponatremia 17 days as against 3.73 days in normonatremic patients .The maximum duration of stay seen in one of the hyponatremic patients was 130 days. A poorer discharge disposition was seen in the hyponatremia group in the study by Rodrigues[43]

In normonatremic stroke patients, an 85% cure rate and 15% death rate was seen. In hyponatremic patients, there was 60% cure and 40% death. This is similar to the death rate reported by Saleem et al, 40%.[15] In both the studies, the presence of hyponatremia was found to significantly alter the treatment outcome in patients with stroke ($p<0.05$)

Kuramatsu et al showed that in-hospital mortality was roughly doubled in hyponatremia compared with nonhyponatremia patients (40.9% vs 21.1%), translating into a 2.5-fold increased odds ratio ($P<0.001$). Also, Multivariable analyses identified hyponatremia as an independent predictor of in-hospital mortality ($P=0.037$)[44].

In the SIADH group, 83% were cured of hyponatremia with treatment and 17% patients succumbed. But in the CSW group, only 25% survived and 75% succumbed to the illness. CSW was significantly associated with higher death rate. ($p<0.05$)

Conclusion

Hyponatremia in the setting of acute stroke occurs in 10-20% patients.

The prevalence is higher in males and among the middle aged.

Hyponatremia, attributed to CSW is more common in stroke patients with sub-arachnoid haemorrhage.

Hyponatremia occurs more with Middle and Posterior cerebral arterial territories involvement.

SIADH has a higher prevalence than Cerebral Salt Wasting.

Hyponatremia and especially, cerebral salt wasting predisposes to a longer duration of hospital stay and poorer discharge disposition.

Hyponatremia, is an independent predictor of short and long term mortality in stroke.

Cerebral Salt wasting has a poorer short term outcome than SIADH.

Thus, a clear distinction between the two entities ought to be made and the appropriate treatment be carried out, to reduce the morbidity, short and long term mortality in acute stroke patients with hyponatremia.

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