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IMPACT OF HYPONATREMIA ON OUTCOME OF ACUTE ISCHEMIC STROKE IN A TERTIARY CARE HOSPITAL.

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ABSTRACT… Objectives: To determine the frequency and impact of hyponatermia on outcome in patients of acute ischemic stroke admitted to a Tertiary Care Hospital, Karachi. **Study Design:** Prospective, cross-sectional, observational study. **Setting:** Department of Medicine, Abbasi Shaheed Hospital, Karachi. **Period:** January 2015 to May 2018. **Material and Methods:** A total of 110 patients of both gender presented with acute ischemic stroke and hyponatermia (2 consecutive serum sodium levels (< 135 mEq/L). Diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting (CSW) was based on predefined criteria. Mortality was considered in terms of modified Rankin Scale with score of 6 within four weeks of admission. Data was analyzed by using SPSS Version 20. **Result:** Out of 110 acute ischemic stroke patients, 66 (60%) were male and 44 (40%) were female. The mean age was 61.45 ± 11.8 years. Mean serum sodium level was 128.4 ± 6.07. Older ages are associated with high mortality rate of 20%. Moderate (29%) and severe (11%) hyponatremia was associated with 21% and 33% mortality respectively. Overall mortality in patients with hyponatremia was 14.5%. **Conclusion:** Mortality rates are higher in acute ischemic stroke patients presented with moderate to severe hyponatremia.

Key words: Acute Ischemic Stroke, Hyponatremia and Mortality.

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INTRODUCTION

Stroke is a debilitating illness and is a leading cause of morbidity and mortality worldwide.[1] Globally burden of stroke is increasingly attributed to preventable and non-preventable risk factors.[2] Similar trends are observed in Pakistan which contributes not only to financial burden on health resources and increasing hospital admissions but also significantly impairs the quality of life.[3] No large scale epidemiological studies are available to highlight the incidence and prevalence of stroke in Pakistan.[4-5] Numerous risk factors are involved in the development of stroke and mortality, such as hypertension, cigarette smoking, electrolyte imbalance, hyperlipidemia and diabetes. [6-7]

Hyponatremia is of special interest because it is a commonly observed condition in patients with acute stroke and has been associated with poor prognosis.[8-9] The cut-off limit for serum sodium in healthy subjects is 135mEq/L.[10] Very mild and subtle symptoms of hyponatremia are often the only presentation, making it a frequently missed condition. [11-12] The symptoms are induced by cerebral edema and possibly adaptive responses of brain cells to osmotic swelling.[13] It is either due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting syndrome (CSW).[14] It is also an important causes of persistent altered sensorium in stroke patients.[15-16] Rodrigues et al found in-hospital mortality in acute ischemic stroke with hyponatremia at 13.5%.[17] Very high prevalence rates, up to 19.1% and very high case fatality rates, up to 42% have been observed for stroke in developing countries like India and Pakistan.[18-20] The study aims to study the frequency and effect of hyponatremia on outcome in ischemic stroke patients in order to establish the local perspective as there is paucity of local data. If found to be significantly high it could be used for routine screening and identification of patients at risk of

high mortality.

MATERIAL AND METHOD

The study was carried out at Department of Medicine, Abbasi Shaheed Hospital, Karachi from January 2015 to May 2018. In this cross sectional study, 110 acute ischemic stroke patients of either gender were included. Ethical approval was obtained from the institute Ethical Review Board regarding data collection and use for research purposes. Patients not consenting and those with chronic diseases like malnutrition, hypothyroidism, chronic kidney disease, chronic liver disease, broncogenic carcinoma ,concurrent pulmonary and CNS infections, patients with history of diarrhea, recent head trauma or surgery and intake of drugs known to cause hyponatermia were excluded. Informed consent was obtained from all the patients for assigning them to sample and using their data in research. History and physical examination was recorded in all patients.

Admission CT scan was done by the radiologist with over five years experience. Physical examination was done to assess muscle power, aphasia, imbalance and GCS and labeled as ischemic stroke. Blood sample was drawn by the researcher in a sterile manner from peripheral vein and collected in specific tube for the measurement of serum sodium level at the time of admission. Hyponatermia was considered if 2 consecutive serum levels were < 135 mEq/L. Severity of hyponatermia was categorized mild (130-134mEq/L), moderate (120-129mEq/L) and severe (<120mEq/L).All selected patients were examined and investigated for the assessment of extracellular fluid volume status in order to differentiate SIADH from CSW syndrome. CSW was diagnosed on the presence following clinical (dry mucous membrane, tachycardia, hypotension, negative fluid balance or CVP < 6 cm of water) and laboratory evidence (raised hematocrit, blood urea/ creatinine or albumin) of hypovolemia. SIADH was considered on the absence of above mentioned clinical and laboratory evidence of hypovolemia. Upon evaluation of the cause of hyponatermia patients with SIADH were treated with fluid restriction whereas those with CSW were given intravenous saline. Fludrocortisone is used in selected patients of CSW. Mortality was labeled in terms of modified Rankin Scale with score of 6 within four weeks of admission by the investigator and recorded. Data was analyzed by using SPSS Version 20. Mean and standard deviation was calculated for quantitative data. Ffrequency and percentages was calculated for qualitative variables. P-value of ≤ 0.05 was considered significant.

RESULT

A total of 350 patients admitted with ischemic stroke were screened for hyponatremia. Informed consent was taken from the patient of the next of kin and after meeting the inclusion and exclusion criteria, 128 patients were followed for the outcome. Out of these, 18 patients left against medical advice and thus 110 (31.4%) patients were included in the final analysis. Sixty-three (57.2%) were males, 47 (42.7%) were females. Thirty-seven (33.6%) were aged 55 or less and 73 (66.4%) were aged more than 55 years, mean age of the patients was 61.45 (± 11.8). Mean serum sodium level was 128.4 (± 6.07). Mild, moderate and severe hyponatremia was found in 66 (60%), 32 (29.1%) and 12 (10.9%) of patients respectively. SIADH was observed in 63 (57.2%) whereas CSW was found in 38 (34.5%) hyponatermic patient, in 9 (8%) patients the cause remain undetermined. Table-I shows associated co morbidities, duration of symptoms and hospital stay. Mean duration of symptoms was 2.5 days SD +/- 2.08. Mean duration of hospital stay was 4.7 days SD+/- 2.06. For outcome, 16 (14.5%) patients expired while 94 (84.5%) patients were discharged back home.

The outcome measure, death or discharge was then stratified according to gender, age, hospital stay, duration of symptoms, and degree of hyponatremia, diabetes mellitus type-2, hypertension and smoking status. (Table-II & III). In male patients mortality was 10.6% compared to 20.5% in females ($p = 0.15$). Only 1 patients younger than 55 year expired (2.7%). Above 55 year age 20.5% of the patients expired ($p = 0.01$).

Among patients who had presented with duration of symptoms 1 day or less 37 (82.2%)

were discharged and 8 (17.8%) expired. Among patients who had duration of symptoms for 2 – 4 days, 47 (87%) were discharged and 7 (13%) expired. Among patients who had symptoms for more than 5 days, 10 (90.9%) were discharged and 1 (9.1%) expired (p-value 0.67). Among patients with length of hospital stay of 3 days or less 17 (56.7%) were discharged, and 13 (43.3%) expired. For those who had stayed for 4 to 5 days 44 (93.6%) were discharged and 3 (6.4%) expired. All of the 33 patients in this study who stayed in hospital for more than 5 days were discharged. When stratified according to the degree of hyponatremia, among patients with mild hyponatremia 7.6% died, among those with moderate hyponatremia 21.9% died, and 33.3% of the patients with severe hyponatremia died. P-value for this was found to be 0.02. (Table-II)

For co-morbids, HTN patients 18.9% mortality compared with 10.5% in non hypertensive patients. Diabetics had 17.3% mortality compared to 12.1% in non diabetics. No difference was seen in mortality among smokers and non smokers as both had 14.5% mortality. The results for co-morbids however were not statistically significant. (Table-III).

Frequency (%)	
Age Group (Years) 55 or less	37 (33.6%)
>55	73 (66.4%)
Smoker	55 (50%)
Diabetics Mellitus	52 (47.3%)
Hypertension	53 (48.2%)
Duration of Symptoms	
1 day or less	45 (40.9%)
2 - 4 days	54 (49%)
5 days or more	11 (10.0%)
Stage of Hyponatremia	
Mild (130-134 mEq/L)	66 (60%)
Moderate (120-129 mEq/L)	32 (29%)
Severe (<120 mEq/L)	12 (10.9%)
Duration of Hospital Stay	
3 days or less	30 (27.3%)
4 -5 days	47 (42.7%)
>5days	33 (30.0%)

Table-I. Patient & laboratory characteristics

Effect Modifiers	Outcome		P-Value
	Death	Discharge	
Male	7 (10.6%)	59 (89.4%)	0.15
Female	9 (20.5%)	35 (79.5%)	
Degree of Hyponatremia			
Mild	5 (7.6%)	61 (92.4%)	0.25
Moderate	7 (21.9%)	25 (78.1%)	
Severe	4 (33.3%)	8 (66.7%)	
Age Group			
55 or less	1 (2.7%)	36 (97.3%)	0.01
>55 yr	15 (20.5%)	38 (79.5%)	
Duration of Symptoms			
1 day or less	8 (17.8%)	37 (82.2%)	0.68
2-4 days	7 (13.0%)	47 (87.0%)	
5 days or more	1 (9.1%)	10 (90.9%)	
Duration of Hospital Stay			
3 days or less	13 (43.3%)	17 (56.7%)	0.000
4-5 days	3 (6.4%)	44(93.6%)	
6 days or more	0	33(100%)	

Table-II. Outcome stratified with patient characteristics

Effect Modifiers	Outcome		P-Value
	Death	Discharge	
Diabetics Mellitus	9 (17.3%)	43(82.7%)	0.43
Hypertension	10 (18.9%)	43 (81.1%)	0.21
Smoking	8 (85.7%)	47 (14.5%)	1.0

Table-III. Outcome stratified with effect modifiers

DISCUSSION

Hyponatremia is a predictive factor for various clinical outcomes and mortality in patients suffering with acute ischemic stroke. In our study, the mean age was 61.45 ± 11.8 years with male predominance, which is similar to study done by Metwally et al.[21] The results from this study show that overall mortality in ischemic stroke patients with hyponatremia is 14.5%. This is a slightly higher value than compared to mortality rates in patients with acute ischemic stroke in general 13%. Several studies show variable frequencies of mortality. It was found to be 13.5% in one study while other studies which showed mortality of 44.2% and 24%.[17-20]

This study also shows, almost double, mortality rate in females compared to males, although

the difference was not statistically significant. Younger patients had lower death rate 2.7% compared to older patients who had mortality rate of 20.5%. This difference is almost tenfold higher in patients with age greater than 55 years and was found to statistically significant. Similarly higher degree of hyponatremia was associated with higher death rates. Mild hyponatremia was associated with 7.6% mortality and on the other hand severe hyponatremia had almost one third of the patients expired 33.3%. It was also noted in our study that, more deaths were observed with shorter duration of hospital stay, while those who survived the initial 3-4 days had good outcome. However no specific pattern of outcome was seen with respect to the duration of symptoms. The results of these findings were corroborated by various studies.[11-20] It may therefore be considered that there may be a true association between the degree of hyponatremia in patients mortality in acute ischemic stroke patients.

Among other co-morbid conditions slightly higher mortality rates were seen with DM and HTN. No difference in mortality was found between smokers and non-smokes in this study, but these results were not statistically significant. Hyponatremia, especially severe hyponatremia, was found in this study to be a much greater risk for mortality compared to DM, HTN or smoking. Since it is also treatable factor, screening early for its presence and adequate correction will result in better clinical outcomes and reduced mortality. Most of the studies evaluated for the co-morbidities showed predominance of hypertension and diabetes mellitus as major contributors to the mortality in stroke patients with hyponatremia.[21-26]

More studies are needed however to quantify the effects of hyponatremia on mortality in acute stroke patients, and to find the mortality benefit that we can get by correcting this factor. Similar studies from other centers in the country are also needed see the overall effect of this in our population from different parts of the country.

CONCLUSION

Mortality rates are higher in acute ischemic stroke patients. In patients with acute ischemic stroke, hyponatremia especially moderate to severe hyponatremia and older age are associated with much higher mortality rates. Higher mortality rates were also observed in females compared to males. Co-morbidities like diabetes mellitus and hypertension showed only slight increase in mortality and need to be managed appropriately. These results suggest hyponatremia to be a prognostic marker of severity of acute ischemic stroke and potential therapeutic target for improving their outcome.

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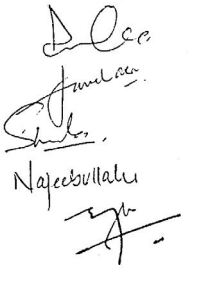
1	Aneela Altaf Kidwai	Study designed, manuscript writing and statistical analysis.	
2	Jamal Ara	Data collection and presentation, secure funding.	
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