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ORIGINAL ARTICLE

Hyponatremia in liver cirrhosis patients presenting with hepatic encephalopathy.

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ABSTRACT… Objective: To determine frequency of hyponatremia in liver cirrhosis patients presenting with hepatic encephalopathy. **Study Design:** Descriptive Cross-sectional study. **Setting:** Department of Medicine, Sandeman Provincial Hospital, Bolan University of Medical and Health Sciences Quetta. **Period:** June 2020 to December 2020. **Material & Methods:** Cirrhosis was characterised on Ultrasound abdomen with altered liver parenchyma, shrunken liver and coarse echo texture. HE was defined as a spectrum of neuropsychiatric abnormalities diagnosed clinically with adequate history taking and physical examination. After taking informed consent from the patients' attendants, 172 patients of liver cirrhosis presenting with HE were enrolled. Detailed clinical history and examination along with investigations were done. Hyponatremia was defined as serum sodium level <135 mEq/L. Data was analyzed through SPSS Version 20.0. **Results:** There were 127 (73.8%) males and 45 (26.2%) females with mean age 46.61±9.31 years while mean BMI was 25.25±2.73 kg/m^2. Out of 172 patients, 18 (10.5%) had Child-Pugh Class A, 63 (36.6%) Child-Pugh Class B and 91 (52.9%) had Child-Pugh Class C. Hospital stay >3 days was seen in 47 (27.3%) while 125 (72.7%) had stay of >3 days. It was observed that 14 (8.1%) patients expired. Hyponatremia was found in 69 (40.1%). **Conclusion:** Hyponatremia was a common feature in liver cirrhosis patients presenting with hepatic encephalopathy. Furthermore a significant association of hyponatremia was seen with hospital stay and all-cause mortality.

Key words: Hepatic Encephalopathy, Hyponatremia, Liver Cirrhosis.

INTRODUCTION

Hepatic encephalopathy (HE) is a potentially reversible complication of liver cirrhosis causing significant mortality.[1] Hyponatremia in cirrhosis has been described since the 1950's but its importance was overlooked for many years and now its role to predict survival in cirrhosis is being investigated.[2] Hyponatremia and HE can occur simultaneously in cirrhosis and the presence of hyponatremia can lead to worsening of HE.[3] Hyponatremia in cirrhosis is caused by hampered renal function to eliminate free water that results in water retention disproportionate to sodium retention leading to reduced plasma osmolarity and is associated with significant morbidity and mortality.[4] The study by Afridi et al.[5] showed hyponatremia to be present in 32.3% with hepatic encephalopathy to conclude that hyponatremia was seen frequently in liver cirrhosis correlating significantly with presence and severity of HE. Our study was undertaken to determine the frequency of hyponatremia among patients of liver cirrhosis with hepatic encephalopathy to provide evidence for hyponatremia as a prognostic factor in HE so that early detection and management of hyponatremia in such patients will help reduce disease burden and mortality in liver cirrhosis.

MATERIAL & METHODS

The objective of present study was to determine the frequency of hyponatremia in liver cirrhosis patients presenting with hepatic encephalopathy. This study was conducted at Medicine Department, Sandeman Provincial Hospital, Bolan University of Medical and Health Sciences Quetta from June 2020 to December 2020. Cirrhosis was characterised by diffuse hepatic fibrosis and nodule formation diagnosed

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on Ultrasound abdomen with altered liver parenchyma, shrunken liver, coarse echo texture with micro and macro nodular formation. Child-Pugh Classification (Table-I) was used to assess severity liver cirrhosis.

HE was defined as a spectrum of neuropsychiatric abnormalities in patients with liver cirrhosis, diagnosed clinically with adequate history taking and physical examination. Serum sodium level <135 mEq/L was labeled hyponatremia. On further division, mild hyponatremia was labeled as 130-134 mEq/L, moderate 125-129 mEq/L and severe <125 mEq/L. The sample size was calculated to be 172 taking margin of error 7% and 95% confidence level.[5]

Criteria	Points		
	1	2	3
Encephalopathy	None	Mild	Severe
Ascites	None	Mild	Severe
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	3.5-2.8	<2.8
INR	<1.7	1.7-2.3	>2.3

Interpretation:
Child-Pugh Class is obtained by adding score of each parameter.
Class A: ≤6 (least severe disease)
Class B: 7-9 (moderately severe disease)
Class C: ≥10 (most severe disease)

Table-I. Child-Pugh classification of liver cirrhosis

Patients with intracranial vascular events (cerebrovascular accidents, vascular malformations, aneurysms and venous sinus thrombosis), infections (meningitis, encephalitis, cerebral abcess spontanous bacterial peritonitis), metabolic problems (hypoglycemia, hyperglycemia, electrolyte imbalance, anoxia, hypercarbia, uremic encephalopathy, wernicke's encephalopathy and toxic encephalopathy), heart failure (EF: < 25%) and chronic renal failure (serum creatinine >3mg/ dl) were excluded from the study. After taking informed consent from the patient's attendants 172 patients of hepatic encephalopathy due to liver cirrhosis as per operational definitions, of both gender aged 20 to 70 years were enrolled in the study using non-probability consecutive sampling technique. Detailed clinical history and examination of the patient was done and blood investigations including liver function tests, coagulation profile and serum electrolytes were carried out. The fluctuations in the values of serum electrolytes were assessed according to their references value. Child-Pugh score was assessed for each patient and recorded.

Statistical Package for Social Sciences (SPSS) Version 20.0 was used for data analysis. Frequencies and percentages were calculated for qualitative variables like gender, Child-Pugh class, hyponatremia, severity of hyponatremia and hospital mortality. Quantitative variables were presented as mean±SD like age, height, weight, BMI, serum sodium level, and length of hospital stay. Effect modifier like age, height, weight, BMI and gender were controlled through stratification. Chi-square test was used to see the effect of modifiers on outcome i.e. hyponatremia in patients with hepatic encephalopathy and p-value ≤0.05 was considered as significant.

RESULTS

A total of 172 patients with liver cirrhosis presenting with HE of both gender aged 25 years to 70 years were evaluated. There were 127 (73.8%) males and 45 (26.2%) females with mean age 46.61±9.31 years. Eighty-seven (50.5%) were aged >45 years while 85 (49.5%) were aged <45 years. Mean weight and height was 71.62±8.52 kg and 168.34±5.55 cm respectively while mean BMI was 25.25±2.73 kg/m^2. On further division, 99 (57.5%) had normal BMI, 64 (37.2%) were overweight, 08 (4.6%) were obese while only 1 patient was underweight. Out of 172 patients, 18 (10.5%) had Child-Pugh Class A, 63 (36.6%) Child-Pugh Class B and 91 (52.9%) had Child-Pugh Class C. Mean hospital stay was 2.82±1.12 days. Hospital stay >3 days was seen in 47 (27.3%) while 125 (72.7%) had stay of >3 days. It was observed that 14 (8.1%) patients expired.

In this study, hyponatremia was found in 69 (40.1%) with mean serum sodium level 135.87±9.44 mEq/L. Of these 69 patients, 18 (26.1%) had mild hyponatremia, 37 (53.6%) had moderate

hyponatremia while severe hyponatremia was seen in 14 (20.3%). Stratification of outcome (hyponatremia) was done with regards to demographic and clinical variables (Table-II) to show a significant association of hyponatremia with hospital stay (p value: <0.001) and all-cause mortality (p value: 0.002).

Variables	Hyponatremia		P-Value
	Present	Absent	
Sex			
Male	48 (37.8%)	79 (62.2%)	0.2097
Female	21 (46.7%)	24 (53.3%)	
Age			
Less than 45 years	34 (40.0%)	51 (60.0%)	0.975
More than 45 years	35 (40.2%)	52 (59.8%)	
BMI			
Underweight	00 (0.0%)	01 (100%)	
Normal	40 (40.3%)	59 (59.7%)	0.872
Overweight	26 (40.6%)	38 (59.4%)	
Obese	03 (37.5%)	05 (62.5%)	
Child-Pugh Class			
Class A	08 (44.5%)	10 (55.5%)	
Class B	28 (44.5%)	35 (55.5%)	0.551
Class C	33 (36.3%)	58 (63.7%)	
Length of Hospital stay			
Less than 3 days	35 (28.0%)	90 (72.0%)	<0.001
More than 3 days	34 (72.3%)	13 (27.7%)	
All-cause Mortality			
Present	11 (78.6%)	03 (21.4%)	0.002
Absent	58 (36.7%)	100(63.3%)	

Table-II. Stratification of outcome (hyponatremia) with regards to demographic and clinical variables (n=172)

DISCUSSION

Cirrhosis is characterized by progressive diffuse and nodular liver fibrosis that leads to loss of normal liver architecture.[6] Complications of cirrhosis are complex and include hepato-renal syndrome, portal hypertension, variceal bleed, spontaneous bacterial peritonitis and hepatic encephalopathy (HE).[7] HE is a potentially reversible complication of liver cirrhosis causing significant mortality.[3] Hyponatremia may induce or exacerbate HE in liver cirrhosis. Hyponatremia is generally attributed to abnormal homeostasis and renal dysfunction to excrete free water leading to water retention unequal to sodium retention and hypo-osmolality.[8] Furthermore, hyponatremia in cirrhosis is linked with a notable reduction in cerebral organic osmolyte concentrations which probably depict compensatory osmoregulatory mechanisms to combat cell swelling caused by a cumulative effect of intracellular accumulation of glutamine due to raised ammonia and low extracellular sodium.[7,8] Various other mechanisms to explain hyponatremia in cirrhosis have been postulated such as raised ANP, reduced renal production of PGE-2 and diminished metabolism of ADH.[10,11]

In our study, hyponatremia was seen in almost 40.1% patients with cirrhosis. Of the 69 patients with hyponatremia in our study 53.6% had moderate hyponatremia, 26.1% had mild hyponatremia while severe hyponatremia was seen in 20.3%. Furthermore a significant association of hyponatremia was seen with hospital stay (p-value <0.001) and all-cause mortality (p-value 0.002). Various studies report hyponatremia in up to half patients of cirrhosis and associating it with poor outcome, longer hospital stay and death.[12,13] In Korea, hyponatremia was seen in 47.9% in hospitalized cirrhosis patients and the severity of hyponatremia associated with higher risk of developing ascites, hepatic encephalopathy and other complications.[14] Another study showed hyponatremia in 57.9% patients with hyponatremia being more common among severe liver failure.[15] Borroni et al.[16] reported hyponatraemia in 30% cirrhosis patients. The study by Afridi et al.[5] showed hyponatremia to be present in 32.3% with hepatic encephalopathy to conclude that hyponatremia was seen frequently in liver cirrhosis correlating significantly with presence and severity of HE. Shaikh et al.[17] reported hyponatremia in 26.7% and it was associated with worse Child-Pugh class, hepatic encephalopathy, severe ascites refractory to paracentesis and the need of high diuretic dosage. Qureshi et al.[1] reported worsening of HE with severing hyponatremia.

The correction of asymptomatic hyponatremia in routine clinical practice has not been recommended.[18] Chief indications for treatment are profound hyponatremia (serum sodium <120 mEq/L) and occurrence of neurologic symptoms

due to hyponatremia.[19] To correct profound hyponatremia, hypertonic saline should be administered in a monitored ICU environment. Hypervolemic/dilutional hyponatremia is ideally treated by fluid restriction and diuretic therapy to increase free water excretion. Hypovolemic hyponatremia is managed by adequate fluid resuscitation to restore circulatory volume and eliminating the causative factor (commonly diuretics). Managing hyponatremia in presence of moderate to severe ascites is difficult as conventional therapies including fluid restriction and loop diuretics are generally inefficacious.[18] Furthermore adhering to fluid restriction is difficult in long-term and ceasing diuretics can worsen ascites. Vaptans selectively antagonize the arginine vasopressin on V_2 receptors in kidney tubules and present aid in treating hyponatremia however they have not been approved due to risk of hepatic failure and increased mortality.[19,20]

Our study is a descriptive non-randomized cross-sectional study and therefore limited due to patient selection bias. A single center-based study having a relatively small sample size, our results may not be generalized to general population. Our study should be used as a stepping stone based on which further studies should be conducted to collect further evidence regarding interactions of hyponatremia with mortality and morbidity in liver cirrhosis and hepatic encephalopathy.

CONCLUSION

Hyponatremia was a common feature in liver cirrhosis patients presenting with hepatic encephalopathy seen in almost 40%. Of the patients with hyponatremia, more than half had moderate hyponatremia with serum sodium levels between 125-129 mEq/L. Furthermore a significant association of hyponatremia was seen with hospital stay and all-cause mortality. We recommend assessment of serum sodium levels in liver cirrhosis patients presenting with hepatic encephalopathy to reduce disease burden and improve survival.

REFERENCES

1. Qureshi MO, Khokhar N, Saleem A, Niazi TK. **Correlation of hyponatremia with hepatic encephalopathy and severity of liver disease.** J Coll Physicians Surg Pak. 2014; 24(2):135-7.
2. Solà E, Watson H, Graupera I, Turón F, Barreto R, Rodríguez E, et al. **Factors related to quality of life in patients with cirrhosis and ascites: Relevance of serum sodium concentration and leg edema.** J Hepatol. 2012; 57:1199–1206.
3. Khan HU, Malik F, Khan Y, Zada S, Ilahi N, Sohail M, et al. **Frequency of hyponatremia and its common complications among patients with hepatic encephalopathy.** Int. J. Biosci. 2017; 10(1):195-201.
4. Afridi MA, Ali Z, Muhammad R, Asghar M, Faheem Afridi M, Bakkar Alam A, et al. **Hyponatremia and its correlation with hepatic encephalopathy in patients with cirrhosis liver.** J Postgrad Med Inst. 2017; 31(3):243-6.
5. Guevara M, Baccaro ME, Torre A, Gómez-Ansón B, Ríos J, Torres F, et al. **Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: A prospective study with time-dependent analysis.** Am J Gastroenterol. 2009; 104:1382–1389.
6. Iwakiri Y, Groszmann RJ. **The hyperdynamic circulation of chronic liver diseases: From the patient to the molecule.** Hepatology. 2006; 43:S121–S131.
7. Poordad FF. **Review article: The burden of hepatic encephalopathy.** Aliment Pharmacol Ther. 2007 Feb; 25 Suppl 1:3-9.
8. Al Sibae MR, McGuire BM. **Current trends in the treatment of hepatic encephalopathy.** Ther Clin Risk Manag. 2009 Jun; 5(3):617-26.
9. Elhassan EA, Schrier RW. **Hyponatremia: Diagnosis, complications, and management including V2 receptor antagonists.** Curr Opin Nephrol Hypertens. 2011; 20:161-8.
10. Adrogué HJ, Madias NE. **Hyponatremia.** N Engl J Med. 2000; 342:1581–1589.
11. Schrier RW. **Water and sodium retention in edematous disorders: Role of vasopressin and aldosterone.** Am J Med. 2006; 119:S47–S53.
12. Angeli P, Wong F, Watson H. **Genes PCAPPS Investigators. Hyponatremia in cirrhosis: Results of a patient population survey.** J Hepatol, 2006, 44, 1535–42.

13. Ginès P, Guevara M. **Hyponatremia in cirrhosis: Pathogenesis, clinical significance, and management.** Hepatology. 2008; 48:1002–1010.

14. Jang CM, Jung YK. **Hyponatremia in Liver Cirrhosis.** Korean J Gastroenterol. 2018 Aug 25; 72(2):74-78. Korean.

15. Cárdenas A, Ginès P. **Predicting mortality in cirrhosis-serum sodium helps.** N Engl J Med 2008; 359:1060-6.

16. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. **Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients.** Digestive and Liver Disease, 2005, 32(7), 605-10.

17. Shaikh S, Mal G, Khalid S, Baloch GH, Akbar Y. **Frequency of hyponatraemia and its influence on liver cirrhosis-related complications.** J Pak Med Ass, 2010,60(2), 116-20.

18. John S, Thuluvath PJ. **Hyponatremia in cirrhosis: Pathophysiology and management.** World J Gastroenterol. 2015 Mar 21; 21(11):3197-205.

19. Wong F, Watson H, Gerbes A, Vilstrup H, Badalamenti S, Bernardi M, Ginès P. **Satavaptan for the management of ascites in cirrhosis: Efficacy and safety across the spectrum of ascites severity.** Gut. 2012; 61:108–116.

20. Ginès P, Wong F, Watson H, Milutinovic S, del Arbol LR, Olteanu D. **Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: A randomized trial.** Hepatology. 2008; 48:204–213.

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