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ORIGINAL ARTICLE

Hyponatremia and its Clinical Outcome Among Patients with Hepatic Encephalopathy Due to Liver Cirrhosis Presenting to ATH Abbottabad

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ABSTRACT

Introduction: Hepatic encephalopathy (HE) is a potentially reversible complication of liver cirrhosis causing significant mortality. 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 osmolality and is associated with significant morbidity and mortality. The purpose of study was to determine the frequency of hyponatremia among patients of liver cirrhosis with hepatic encephalopathy.

Methods: The design of this study was an observational study design which was hospital-based survey and was conducted on 130 patients of liver cirrhosis. A specialized questionnaire was designed to collect all the study information. All data was analyzed using SPSS Statistics version 24. Chi-square test and Spearman's rank test were employed to correlate hyponatremia with HE and its severity. A p-value of <0.05 was considered statistically significant.

Results: Among the patients, 92 (71%) males and 38 (29%) females; the mean age of the patients was 56±11.3 years. Hyponatremia was present in 48 (36.9%) patients. Among these, 25 (52%) were male and 23 (48%) were female; 12 (25%) patients had mild Hyponatremia, 28(58.3%) had moderate, and 8 (16.6%) had severe Hyponatremia. HE was significantly associated with hyponatremia with p value of lea than 0.001.

Practical Implication: The benefit of 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.

Conclusion: Patients with lower levels of sodium had higher grades/severity of HE. Significant association of hyponatremia was seen with liver cirrhosis and encephalopathy.

Keywords: Abbottabad, Cirrhosis, Hepatic encephalopathy, Hyponatremia, Liver.

INTRODUCTION

Hyponatremia is disturbance in total body water regulation leading to decreased clearance of solute free water and the consequent inability to match the urine output to the amount of water ingested leading to hyponatremia [1,2,3,4]. Hyponatremia is most common electrolyte disorder in hospitalized patients and more so in cirrhosis patients. Hyponatremia in cirrhosis is defined as a serum sodium level of less than 130 meq/L Patients with cirrhosis may develop hyponatremia due to either hypovolemia which is because of loss of extracellular fluid due to diuretics or hypervolemia which is expanded extracellular fluid volume due to the inability of the kidneys to excrete solute-free water proportionate to the amount of free water ingested [4,5]. A disturbance in total body water regulation leading to decreased clearance of solute free water and the consequent inability to match the urine output to the amount of water ingested leads to dilutional hyponatremia [6,7,8].

Hepatic encephalopathy (HE) is a potentially reversible complication of liver cirrhosis causing significant mortality [9,10,11,12,13]. 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 [14,15]. 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 [16,17]. 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. According to this hypothesis, hyperammonemia in cirrhosis would cause an increased intracellular content of glutamine, because astrocytes have glutamine synthase, which is the only cerebral pathway capable of detoxifying ammonia. increased glutamine content in the astrocytes would result in an increased intracellular osmolality that would lead to the passage of fluid from the extracellular to the intracellular compartment. Astrocyte swelling would result in astrocyte dysfunction, mainly as a result of increased oxidative stress, which would facilitate development of HE. Evidence for the existence of this low-grade cerebral edema is derived from experimental and human studies using magnetic resonance methods to indirectly evaluate water content in the brain, including magnetization transfer ratio and diffusion-weighed imaging (9 – 12).

In this context of deranged osmotic balance in the cirrhotic brain, the development of hyponatremia could represent a second osmotic hit to the astrocytes that could aggravate the intracellular edema by causing a further shift of water from the extracellular to the intracellular compartment and facilitate HE. Support for this assumption is derived from experimental studies showing that rats with chronic hyponatremia and portocaval anastomosis develop greater brain edema after an ammonia load compared with normonatremic rats, and from human studies showing that both ammonia and serum sodium levels are major determinants of electroencephalographic abnormalities in patients with cirrhosis (13,14). Nevertheless, no studies have been carried out to specifically evaluate a possible association between serum sodium levels and development of HE in patients with cirrhosis. - therefore, this study was undertaken to evaluate prospectively the relationship between serum sodium levels and the occurrence of overt HE in a series of patients with cirrhosis. Moreover, in addition to serum sodium concentration, a number of other variables that may have an influence on HE was also analyzed. Considering that serum sodium concentration, as well as other variables of the liver and renal function may change over time and that HE is frequently a recurrent event, the statistical approach used in this study was a time dependent analysis, which takes into consideration the values of the different variables obtained at several time points during the study. - is type of approach allows for a better assessment of the relationship between laboratory variables and a specific event compared with the standard time-independent approach which only takes into consideration values obtained at the beginning of the study.

MATERIAL AND METHODS

The design of this study was an observational study desing and this study was and this study was a hospital-based survey and was conducted on 130 patients of liver cirrhosis admitted to our tertiary care hospital during the study period of 18 months from January 2021 to September 2022. Informed consent was obtained from all patients enrolled for the study.

Data Collection: The data of the patients was collected in a well-designed pro forma (consisting of the patient's particulars, detailed history, clinical examination and investigations).

Inclusion Criteria: The status of the patients at the time of inclusion (inpatient or outpatient) Patients with diagnosed hepatic cirrhosis of any etiology who were aged between 20-80 years were included in this study.

Exclusion Criteria: Patients under treatment for hepatocellular carcinoma, ascites, and hyponatremia were excluded. Patients with underlying renal pathology, those on dialysis, and patients on diuretic therapy were also excluded. After taking relevant history and physical examination, the venous blood sample of each patient was drawn and sent to the institutional laboratory for estimation of serum electrolytes, liver function tests (LFTs), renal parameters (RPMs), prothrombin time (PT), activated partial thromboplastic time (aPTT), and international normalized ratio (INR). We classified the HE according to the West Haven classification system. Mild to moderate encephalopathy was classified under grades I-II, while severe encephalopathy was classified under grades III-IV. We documented the severity of liver disease according to the Child-Pugh score criteria. The patients were classified into different groups based on the serum sodium concentration as follows: level of <130 meql/l (significant/severe hyponatremia), between 131 and 135 meq/l (mild hyponatremia), and level of >135 meq/l (normal). A specialized questionnaire was designed to collect all the study information. All data was analyzed using SPSS Statistics version 24. We reported the data as means along with standard error. Frequencies and percentages were calculated for gender, hyponatremia, and the presence of HE. Chi-square test and Spearman's rank test were employed to correlate hyponatremia with HE and its severity. A p-value of <0.05 was considered statistically significant.

RESULTS

Among the total 130 patients, there were 92 (71%) males and 38 (29%) females; the mean age of the patients was 56±11.3 years. Overall, serum sodium levels among the subjects ranged from 115 to 142 meq/L, with a mean of 129.11 ±6.53 meq/L. In patients with hyponatremia, it ranged from 115 to 127 meq/L (mean: 121.41 ±5.17 meq/L). Hyponatremia was present in 48 (36.9%) patients. Among these, 25 (52%) were male and 23 (48%) were female; 12 (25%) patients had mild hyponatremia, 28(58.3%) had moderate, and 8 (16.6%) had severe hyponatremia.

Table 1: Hepatic Encephalopathy Association with Hyponatremia

Hyponatremia	Hepatic encephalopathy		Total	Significance
	Yes	No		
Yes	42	6	48	P-value: <0.001
No	46	36	82	
Total	88	42	130	

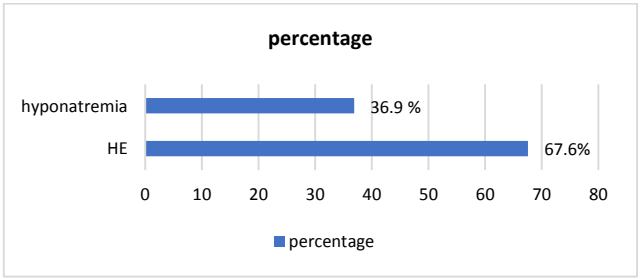

Figure 1: Percentages of hyponatremia and HE

HE was present in 88 (67.6%) patients. HE grades I was present in 27(30.6%), grade II in 31 (35.2%), grade III in 16 (18.8%), and grade IV in 14 (15.9%) patients. In 48 patients with hyponatremia, 42 were found to have HE (p-value: <0.001). The association of hyponatremia with HE is shown in Table.

Table 2: Severity Of Hyponatremia And Grades Of Hepatic Encephalopathy

Severity Of Hyponatremia	Grades Of Hepatic Encephalopathy						Significance
	I	II	III	IV	None	Total	
Mild	4	3	2	1	2	12	P-value: <0.001
Moderate	11	9	3	1	4	28	
Severe	1	1	3	3	0	8	
none	11	18	8	9	36	82	
Total	27	31	16	14	42	130	

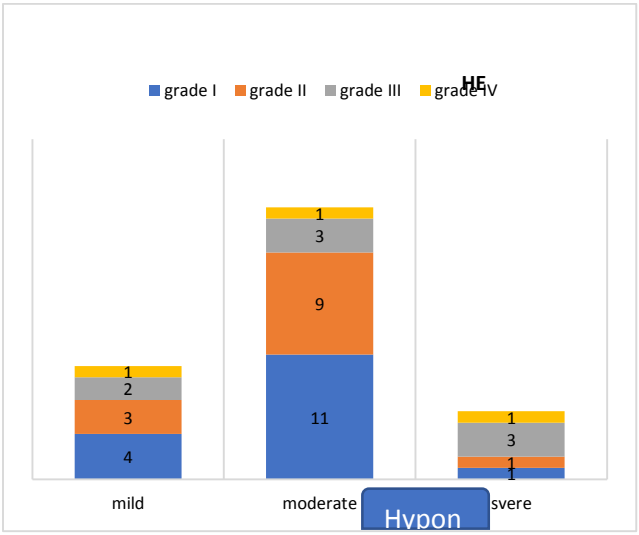

Figure 2: Association Between HE Grades and Hyponatremia Severity

DISCUSSION

Study shows HE was seen to be correlated with hyponatremia which is found previously in many studies including results similar to results of Shaikh et al. [18] reported hyponatremia in 26.7% and it was associated with worse hepatic encephalopathy, severe ascites refractory to paracentesis and the need of high diuretic dosage. Qureshi et al. [19] reported worsening of HE with severing hyponatremia. The risk of developing ascites, variceal bleeding, HE, and other cirrhosis-related complications is directly proportional to the degree/severity of hyponatremia. Various studies have shown that severe hyponatremia is associated with increased severity of HE [20] which supports our study and other also see higher grades of hepatic encephalopathy and hypernatremia show association with one another. The association between HE and hyponatremia may be explained based on the higher severity of liver disease among patients with sodium levels of <130 meq/L and the hypothesis that there might be a pathophysiological link between these two events. In a study by Cordoba et al., it was concluded that hyponatremia causes mild cerebral edema, which results in increased osmotic pressure on astrocytes. Eventually, it leads to many neurological dysfunctions [21]. Hyponatremia and encephalopathy are interlinked and found to be associated with one another.

In addition to hyponatremia, serum bilirubin was also found to be an independent predictive factor of the development of overt HE. This finding was not unexpected as serum bilirubin is known to be an excellent marker of liver function and HE is related to the severity of liver failure [7 – 9] . In earlier studies assessing predictive factors of HE, serum bilirubin was either not included as a specific variable in the analysis (yet it was included as a component of the Child – Pugh score) or did not show a predictive value [22,23]. The reason for the discrepant findings between these studies and the

current investigation may be because of the fact that in this study, serum bilirubin was analyzed as a time-dependent variable, so that values of serum bilirubin obtained at several time points were included in the analysis, whereas in earlier studies, only the value of serum bilirubin obtained at the baseline was analyzed for its association with HE. Serum creatinine was also found to be an independent predictive factor of overt HE. In clinical practice, it is very common that patients with advanced cirrhosis and renal failure have associated HE. Nevertheless, to our knowledge, the finding of an independent association between serum creatinine levels and the occurrence of overt HE has not been reported earlier [(24)]. Two possible explanations could be accounted for such an association. First, serum creatinine levels may be indicative of advanced liver disease without a direct cause – effect relationship with HE. - is possibility is unlikely because the value of serum creatinine was independent from that of serum bilirubin and there was no interaction between these two variables. Second, considering that renal failure in patients without liver disease may effect cerebral function, the possibility exists of a direct effect between impaired renal function and HE. - is possibility deserving investigation in future studies. Finally, as shown in earlier studies [(3,2)], an earlier history of overt HE was also an independent predictive factor of the occurrence of overt HE

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 can be used as a steppingstone 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 [(22,23)]. Further studies can be conducted to find out the cause of hyponatremia and further evaluation can be done to see the because of low levels of hyponatremia. Studies can also be conducted to see the cause of mild higher levels of hyponatremia. Causes for association between hyponatremia and hepatic encephalopathy can be studied. Cause for higher level hyponatremia with grading of hepatic encephalopathy can also be studied.

CONCLUSION

Patients with lower levels of sodium had higher grades/severity of HE. Significant association of hyponatremia was seen with liver cirrhosis and encephalopathy.

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