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HEPATIC ENCEPHALOPATHY;

HYPONATREMIA IN LIVER CIRRHOSIC PATIENTS WITH HEPATIC ENCEPHALOPATHY

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ABSTRACT… Objectives: To determine the prevalence and relation to severity of hyponatremia in liver cirrhotic patients associated with hepatic encephalopathy. **Study Design:** Cross sectional study. **Place and Duration of Study:** Medicine Department of Peoples University of Medical and Health Sciences Nawabshah from 26th October 2016 to 25th April 2017. **Material and Methods:** All patients of either gender with 15 to 70 years associated liver cirrhosis, were included in the study. Diagnosis of liver cirrhosis was confirmed by laboratory and ultrasonographic findings. Exclusion criteria were patients outside of patient range, patients with hepatocellular carcinoma, or anotherco morbid. Sodium levels were measured by 2cc blood sample by blood from cubital vein preferably. Encephalopathy was evaluated via West Haven classification. All the data were entered into SPSS 20 version and were analyzed by using the same software. **Results:** A total of 369 patients met the inclusion criteria. Among them were 129 males and 240 females. The overall mean age of study subjects was 57.07±9.23 years. The overall mean duration of hepatic encephalopathy was 2.53±0.733 days. The overall mean serum sodium level for study subjects was 129.59±7.11 mEq/L. Most of the study subjects, 83.5% had HCV, 12.7% patients were HBV positive whereas 3% were positive for HBV as well as HCV. 26 patients had grade 1 encephalopathy, 30 patients had grade II encephalopathies, 258 patients had grade III encephalopathies, and 55 patients had grade IV encephalopathy. In our study, 73.2% study subjects were observed with hyponatremia. Out of 270 study subjects found with hyponatremia, 25.2% had mild hyponatremia, 44.8% had moderate hyponatremia, and 30% had severe hyponatremia. The results showed that there was a significant association of hyponatremia with viral markers (p=0.030), duration of hepatic encephalopathy (p=0.102) and grades of hepatic encephalopathy (p=0.746). **Conclusion:** We concluded hyponatremia is frequently found in patients with cirrhosis liver. Significant correlation of hyponatremia with the severity of hepatic encephalopathy.

Key words: Hyponatremia, Liver Cirrhosis, Hepatic Encephalopathy, Chronic Liver Diseases.

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INTRODUCTION

Pakistan is a developing country having high prevalence of hepatitis B and C that accounts for a large number of patients progressing to chronic liver disease. Advance cirrhotic patients presents with a number of complications like hepatorenal syndrome, spontaneous bacterial peritonitis and hepatic encephalopathy. Disturbance in body water homeostasis is one of its manifestations. There are so many factors accounting for the disturbance in total body water homeostasis for hyponatremia.

Hyponatremia is a crucial prognostic factor in the outcome of chronic liver disease.[1] Sodium is the main electrolyte defining serum osmolarity. Hyponatremia is labeledwhen serum sodium concentration is below136 mEq/L. However, in the presence of cirrhosis hyponatremia is diagnosed if serum sodium concentration falls below the level of 130 mEq/L.[2] Hyponatremia can be broadly classified into hypovolemic, euvolemic and hypervolemic hyponatremia. Most common category of hyponatremia occurs in cirrhosis is dilutional hyponatremia. Some other conditions in which dilutional hyponatremia can be seen include congestive cardiac failure, nephritic syndrome and renal failure.[3] The pathogenesis of

cirrhosis involves the release of vasodilators such as nitric oxide, substance P, various endotoxins and endogenous cannabinoids which drop effective arterial volume and leading to activation of renin-angiotensin aldosterone axis and ADH mediated free water absorption. Another type of hypovolemia present in cirrhosis is hypovolemic hyponatremia, resulting from loss of ECF mainly from kidneys due to excessive diuresis and also from the gastro-intestinal tract. Other features of this kind of hyponatremia comprise low serum sodium beside contracted plasma volume without any sign of edema and ascites. It can also exist with features of pre-renal renal failure.[4]

Encephalopathy develops when there is dysregulation in the normal neuronal environment including a well-adjusted quantity of fluids, electrolytes, nutrients, amino acids, and neurotransmitters. Increase or decrease in these substances can alter the role of ascending reticular activating system and leading to compromised awareness.[5] The histological features in the brain in patients with hepatic encephalopathy and hyponatremia comprise astrocyte injury. The macroscopic findings apparent with neuro-imaging reveals brain edema. Acute stage may be a confusional condition with or without nausea.[6] Hyponatremia aggravates the alteration in osmolality among intracellular and extracellular milieu. Astrocytes compensate the osmotic variances by reducing intracellular levels of organic osmolytes like choline compounds, glutamate, and myo-inositol. A reduction in myo-inositol describes the incompetence of astrocytes to handle augmented ammonia burdenas they oppose the accumulation of glutamine.[7] Many situations such as hemorrhage, benzodiazepines and sedatives can deteriorate hepatic encephalopathy as these situations precipitate astrocyte swelling.[8] Cirrhotic patients with hyponatremia moreover reveal resistance to treatment with lactulose even with slight hepatic encephalopathy. Improvement of hyponatremia can have a positive effect on the prognosis of these cases. The degree of hyponatremia determines the severity of symptoms. At levels 125-130 mEq/L. When serum sodium levels drop below 115-120 mEq/L severe signs such as a headache, obtundation and lethargy are present. Extremely severe patients may present as coma or respiratory arrest.[9]

METHODS

This is a cross-sectional study conducted in Nawabshah at the department of medicine, Peoples University of medical and health sciences for women, Pakistan. The study duration was six months starting from 26th October 2016 to 25th April 2017. Inclusion criteria comprised of all diagnosed cases of liver cirrhosis both males and females with age between 15-70 years. All patients were exhibiting features suggestive if hepatic encephalopathy within five days of data collection. Diagnosis of liver cirrhosis was made on the basis of the laboratory as well as ultrasonographic findings. Exclusion criteria comprised of all patients outside our age range. Informed consent was taken from patients prior collecting data and patients who were not giving consent were excluded from the study. Patients with hepatocellular carcinoma secondary to cirrhosis were excluded from the study. Serum alfa protein was measured as a marker for hepatocellular carcinoma. For confirmation of hepatocellular carcinoma, liver biopsy was performed. Patients with exudative ascites were excluded from the study. Patients with co-morbid such as type 1 or 2 diabetes mellitus, hypertension, chronic kidney disease or congestive heart failure were excluded from the study.

Detailed history, clinical examination and various routine and necessary investigations were done in all subjects with usual aseptic measures. A 2cc blood sample was collected from the cubital vein into a 5cc disposable syringe for serum sodium estimation, and sent to diagnostic and research laboratory for analyses. The frequency of hyponatremia was evaluated while the HE was graded according to the West Haven classification. Grades I-II were taken as mild to moderate encephalopathy, while grades III-IV were taken as severe encephalopathy. The demographic profile of the patient was noted. The serum sodium [Na+] level 135-145mmol/L was taken as normal and the value <135 was labeled as hyponatremia. The severity of hyponatremia was categorized

as: mild, moderate, and severe. All the data regarding age, gender, serum sodium level, grades and duration of hepatic encephalopathy were recorded on proforma attached.

All the data were entered into SPSS 16 version and were analyzed by using the same software. The quantitative data like age, duration of hepatic encephalopathy, serum sodium level were presented in form of mean±SD. Simple frequency and percentage were computed for the gender, virology, grades of HE and hyponatremia. Stratification with respect to the age, gender, grades and duration of HE and viral markers were done to control the effect modifiers. Chi-Square test was applied and P-value <0.05 was considered as significant.

RESULTS

A total of 369 patients met the inclusion criteria. Among them were 129 males and 240 females (Figure-1). The overall mean age of study subjects was 57.07±9.23 years. Patients are divided into two age groups. Those below 60 years of age and those above 60 years of age. 195 (53%) patients were below 60 years of age. 174 (47$) patients were aboe 60 years of age. This is shown in Table-I. The overall mean duration of hepatic encephalopathy was 2.53±0.733 days. This is shown in Table-II. The overall mean serum sodium level for study subjects was 129.59±7.11 mEq/L. Most of the study subjects, 83.5% had HCV, 12.7% patients were HBV positive whereas 3% were positive for HBV as well as HCV. This is shown in Figure-2.

	<60 years (n=195)	**≥ 60 years** (n=174)
Mean±SD	51.58±9.66	63.22±2.16
95%CI	50.22-52.94	62.90-63.55
Median (IQR)	56.00 (10)	63.00
Range	40	7
Minimum	19	60
Maximum	59	67

Table-I. Descriptive statistics of age according to age groups

	≤3 days (n=351)	**>3 days (n=18)**
Mean±SD	2.43±0.59	4.44±0.51
95%CI	2.37-2.50	4.19-4.69
Median (IQR)	2.00 (1)	4.00 ()
Range	2	1
Minimum	1	4
Maximum	3	5

Table-II. Descriptive statistics of duration of hepatic encephalopathy according to stratified groups

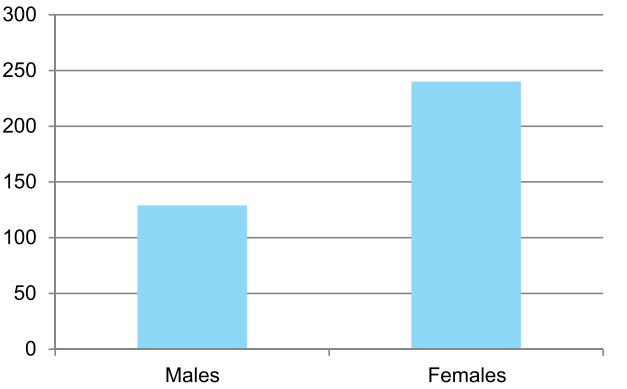

Figure-1. Frequency of patients according to gender

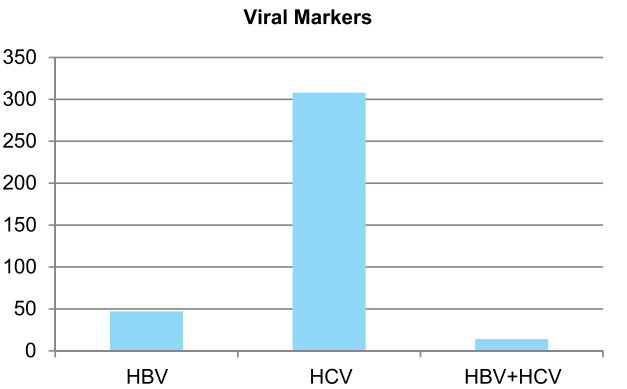

Figure-2. Frequency distribution of viral markers (n=369)

26 patients had grade 1 encephalopathy, 30 patients had grade II encephalopathies, 258 patients had grade III encephalopathies, 55 patients had grade IV encephalopathy. Grade-III was found most common grade which was found in 69.9% study subjects. This is shown in Figure-3. In our study, 73.2% study subjects were observed with hyponatremia. Out of 270 study subjects found with hyponatremia, 25.2% had mild hyponatremia, 44.8% had moderate hyponatremia, and 30% had severe hyponatremia as presented in Figure-4. The frequency of

distribution of hyponatremia according to gender and age are shown in Figure-5 and 6.

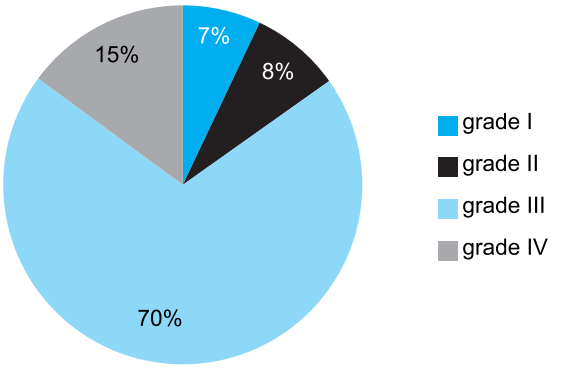

Figure-3. Frequency distribution of hepatic encephalopathy

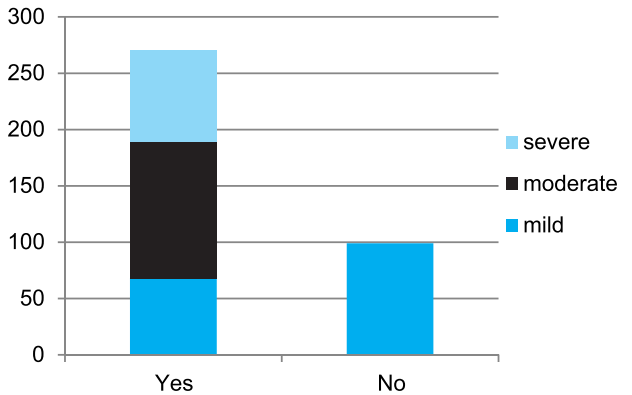

Figure-4. Frequency distribution of hyponatremia

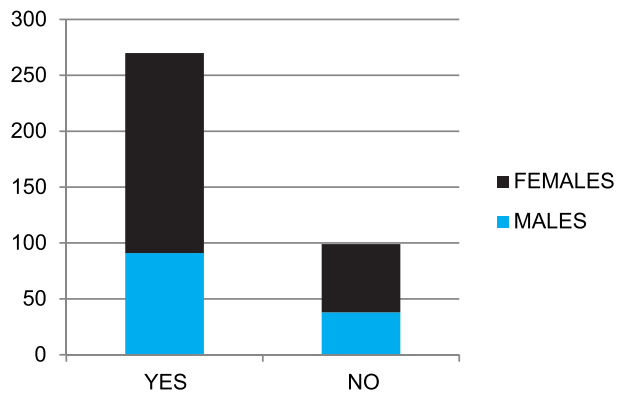

Figure-5. Frequency distribution of hyponatremia according to gender

The results showed that there was a significant association of hyponatremia with viral markers (p=0.030). While no significant association was observed with gender (p=0.404), age (p=0.586), duration of hepatic encephalopathy (p=0.102) and grades of hepatic encephalopathy (p=0.746).

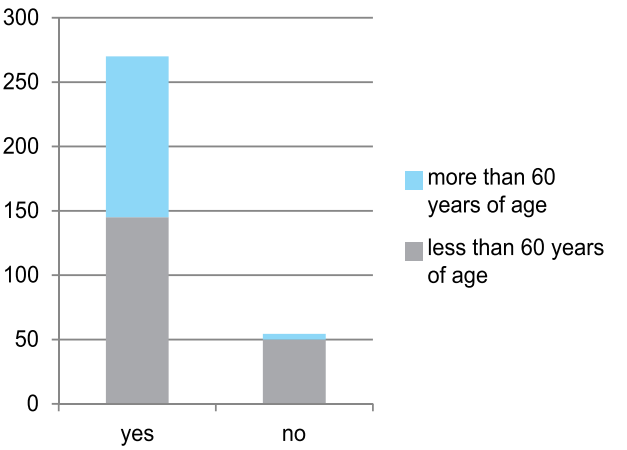

Figure-6. Frequency of distribution of hyponatremia according to age (p = 0.058)

DISCUSSION

A recent report on 997 cirrhotic patients demonstrated the presence of hyponatremia (serum Na concentration <130 mEq/L) in 21.6% patients. Moreover, cirrhosis related complications such as hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis were more prominent in these patients.[10] Another study conducted on 523 cirrhotic patients with ascites demonstrated that health-related quality of life was significantly decreased in patients with serum sodium concentration less than 130 mEq/L.[11] It has been demonstrated that patients with hyponatremia have resistance to treatment with diuretics and a higher incidence of refractory ascites and therapeutic paracentesis.[12]

A time dependent statistical analysis among patients with cirrhosis have shown hyponatremia as an independent predictor of hepatic encephalopathy.[13] Serum ammonia levels and serum sodium levels play a major role in predicting electroencephalographic abnormalities among cirrhotic patients.[14] It has also been found that hyponatremia can worsen hepatic encephalopathy in patients undergoing TIPS.[15] Patients with hepatic encephalopathy along with hyponatremia are at increased risk for development of brain edema and eventually herniation.[16]

Therapy for hyponatremia is challenging because

rapid correction can be potentially fatal. The brain has adapted to protect itself from cerebral edema. Therefore correction of hyponatremia should be done over a long period to protect it from osmotic demyelination syndrome. Plasma sodium concentration should be elevated at a rate of 10-12 mEq/L on the first day and over 18 mEq/L on next two days.[17] Chronic mild hyponatremia should also be corrected over time as it may be asymptomatic but is associated with future improvement of the quality of life.[18] As the role of vasopressin in the development of hyponatremia is well-known, drugs known as vaptans have been developed. These are specific antagonists of the V2 AVP receptors. Vaptans enables restoration of solute-free water and normalizes hyponatremia.[4]

The results of our study are similar to results of Khan et al's study and Akbar et al's study.[19,20] Khan et al's study report 72% cirrhotic patients with hyponatremia. 27.8% had mild hyponatremia whereas 41.7% had moderate hyponatremia while 30.6% had severe hyponatremia. Akbar et al's study also report 72% cirrhotic patients with hyponatremia. Angeli et al also classified patients with mild, moderate and severe hyponatremia. 50.6% patients had mild hyponatremia, 27.8% had moderate hyponatremia and 21.6% had severe hyponatremia. 17% of patients with severe hyponatremia had the hepatorenal syndrome, 10% of patients with moderate hyponatremia had hepatorenal syndrome whereas 6% patients with normal serum sodium concentration had hepatorenal syndrome.[21]

Patients awaiting liver transplant with hyponatremia have also been shown to have poorer outcomes when compared with patients with normal sodium levels. Using data derived from the Organ Procurement and Transplantation Network, Kim et al. developed and validated a survival score that included serum sodium in the model for an end-stage liver disease (MELD-Na).[22] Serum sodium was found to independently predict mortality with an HR of 1.05 per mmol decrease in serum sodium between 125 mmol/L and 140 mmol/L. The combination of MELD and serum sodium was significantly higher than MELD score alone in 7% of patients who died within 3 months of being listed for transplantation. This result suggested that there was a subgroup of patients that would benefit from gaining sodium-based exception points that may expedite time to transplantation. Hyponatraemia was also recently shown to predict mortality in the first 90 days after listing for transplant in a pediatric population.[23] Moreover, patients undergoing surgery with hyponatremia are prone to develop irreversible neurologic damage, renal failure, longer duration of hospital stay and are at increased risk for bacterial infections.[24]

CONCLUSION

Hyponatremia is frequently found in patients with cirrhosis liver. Significant correlation of hyponatremia with the severity of hepatic encephalopathy. Therefore, all patients with liver disease should be investigated with hyponatremia to identify patients at high risk of complications including hepatic encephalopathy.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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1	Ashok Kumar Lohano	Conceived designed, Manuscript editing, Final approval.	
2	Shamsuddin Shaikh	Introduction, Statistical analysis, Discussion.	
3	Nazia Arain	Literature search and review, Bibliography.	