Original Research Article

Clinical study on correlation between serum sodium levels and serum ammonia levels in relation with hepatic encephalopathy in patients with cirrhosis of liver

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Abstract

Cirrhosis is a progressive, diffuse fibrotic process in the liver, leading to nodule formation and disruption of the normal architecture. Well compensated cirrhosis can remain asymptomatic for many years until a decompensating event occurs, such as ascites, spontaneous bacterial peritonitis, variceal hemorrhage or hepatic encephalopathy. Here, we have conducted study on 41 patients with decompensated liver disease from October 2018 to March 2019. Our main aims and objectives were to correlate relation between serum sodium levels and hepatic encephalopathy and also correlation between serum sodium and serum ammonia levels in patients with hepatic encephalopathy (HE). We observed 61% of patients had hyponatremia. 11(26%) patients had features of hepatic encephalopathy. Mean sodium of 127meq/dl in patients with HE. There were raised serum ammonia levels in patients with HE.

Key words

Hyponatremia, Cirrhosis of liver, Hepatic encephalopathy, Ammonia.

Introduction

The liver is the largest organ in the body and one of the most complex functioning organs with a wide array of functions. It plays a major role in carbohydrate, protein, lipid metabolism along with, also has role in inactivation of various toxins, metabolism of drugs, hormones, synthesis of plasma proteins and maintenance of immunity (Kupffer cells). Chronic parenchymal liver disease is one common medical disease encountered in medical wards in day to day practice. Portal hypertension is responsible for most of the complications that mark the transition from compensated to decompensated cirrhosis. Intractable ascites, edema, hematemesis, hepatopulmonary syndrome and hepatorenal syndrome are common clinical presentations in these patients. Severe hyponatremia, and decreased arterial pressure are clinical findings seen in patients with advanced cirrhosis [1].

Hyponatremia is common in cirrhosis. It occurs in an advanced stage of the disease and is associated with complications and increased mortality. Either hypovolemic or, more commonly, hypervolemic hyponatremia can be seen in cirrhosis. Impaired renal sodium handling due to renal hypoperfusion and increased arginine-vasopressin secretion secondary to reduced effective volemia due to peripheral arterial vasodilation represent the main mechanisms leading to dilutional hyponatremia in this setting. Patients with cirrhosis usually develop slowly progressing hyponatremia. In different clinical contexts, it is associated with neurological manifestations due to increased brain water content, where the intensity is often magnified by concomitant hyperammonemia leading to hepatic encephalopathy [2].

Hyponatremia in cirrhosis is due to an impairment in the renal capacity to eliminate solute-free water that causes a retention of water that is disproportionate to the retention of sodium, thus causing a reduction in serum sodium concentration and hypoosmolality. There have been many other causative factors has been explained for hyponatremia, main pathogenic factor responsible for hyponatremia is a non-osmotic hypersecretion of arginine vasopressin (or antidiuretic hormone) from the neurohypophysis related to circulatory dysfunction [3, 4].

In cirrhosis presence peripheral vasodialatation triggers activation of the renin angiotensin system and sympathetic nervous system, which leads avid sodium and water retention with increased antidiuretic hormone release, resulting in dilutional hyponatremia [5].

In chronic liver disease, hyponatremia it acts as a key prognostic factor in patients with liver cirrhosis when hyponatremia was incorporated into the MELD score Hyponatremia is a common abnormal finding in approximately 57% of hospitalized patients with chronic liver disease [6].

HE is a neuropsychiatric syndrome with unclear etiology. There are several precipitating factors has been explained, among which electrolyte imbalance is one of the factor which is responsible for aggravating HE. Ammonia is the key element which acts on the brain and is considered central to the pathogenesis of HE. Along with hyperammonemia, presence of hyponatremia lowers the levels of myo-inositol in the astrocytes resulting in cerebral edema and development of overt HE. Hyponatremia in cirrhosis is associated with a high morbidity and mortality and like ammonia, is a marker for poor prognosis in patients with cirrhosis and also in development of cirrhosis related complications [7, 8, 9].

Hyponatremia per se can produce a variety of neurological disturbances including muscle weakness, seizures, cognitive impairment, and coma, and its contribution towards development of hepatic encephalopathy through osmolar changes in brain astrocytes and neurons [10]. The risk of waitlist mortality appears to increase by 12% for each unit of decrease in serum

sodium concentration for values between 120 and 135 mmol/L. Hence, Ammonia and hyponatremia result in low grade cerebral edema leading to HE which is clinically manifested by attention deficits, alterations in sleep patterns, muscular in-coordination ultimately progressing to stupor, coma and seizures [11].

This study was done to find the effect of both serum ammonia and hyponatremia on the development of HE in patients with cirrhosis of liver presenting to a tertiary care hospital.

Materials and methods

This was an Analytical descriptive study done at Raja Rajeswari Medical College and Hospital, from October 2018 to April 2019.

Patients with clinical diagnosis of chronic liver disease from medical wards and medicine outpatient department were included in the study. Informed written consent was obtained from participants of the study. Institutional ethical committee clearance was obtained before the study.

Inclusion criteria

- Patients with clinical diagnosis of chronic liver disease.
- Patients with ultrasound diagnosis of cirrhosis.
- Age group between 18 -55years.

Exclusion criteria

- Patients with Encephalopathy because of Renal failure, Hypertension, Sepsis, CNS infections (Meningitis, Encephalitis), patients on diuretics, patients diagnosed with hepatocellular carcinoma.

Ethical committee clearance was obtained before study.

Patients who met with inclusion criteria were subjected for ultrasound abdomen examination. Various blood tests were done including liver function tests, complete hemogram, peripheral blood smear, markers for viral hepatitis, transthoracic Echo cardiography and doppler study, prothrombin time, serum ammonia levels. Venous blood was analyzed for the measurement of Serum ammonia and Serum sodium levels within the first hour of admission.

Results were analyzed by suitable statistical parameters.

Results

We conducted study on 42 patients with chronic liver disease diagnosed clinically and by ultrasound abdomen. This was an observational non-interventional correlational clinical study. Maximum number of patients was in 41-50 years and 30-40 years of age groups. Only 6 patients were above 50 years. Eighty-eight percent of patients were males and 12% were female. Alcohol consumption (38 patients) was common etiology for all these patients and 3 patients had cirrhosis of cryptogenic origin. Fifty percent of patients had history of alcohol consumption for more than 10 years. Ascites, jaundice, generalized weakness and edema of limbs were common symptoms at admission. We observed 17(41%) patients had sodium levels between 125-130 meq/dl and 10 (24%) patients had serum sodium between 130-135meq/dl (**Table - 1**). Mean serum sodium was 133meq/dl in patients without features of hepatic encephalopathy. We observed frequency of hepatic encephalopathy in 11(26%) patients and hyperammonemia was observed in all these patients (**Table – 2, 3**). Ascites was observed in majority of patients, edema, jaundice was observed in few patients along with features of hepatic encephalopathy (**Table - 4**). 90% of patients with features of HE had child pugh's grade B and C. Only one patient had grade A (**Table - 5**). It was strongly observed that patients with hyponatremia had high MELD score above 20%. Mean sodium in patients with above 20-30% was 130 meq/dl and 127 meq/dl in patients with score above 30% (**Table – 6, 7**) which was statistically significant. Majority of these patients with MELD score above 20% had low mean platelet count, prolonged prothrombin time and prolonged INR. Patients with hyponatremia showed significant

development of other complications like ascites, hepatic encephalopathy, high risk of gastrointestinal bleed, anemia, thrombocytopenia. Hence, dilutional hyponatremia acts as a key prognostic factor in patients with cirrhosis.

Table - 1: Serum electrolytes distribution of patients studied.

	No. of patients (n=41)	%
Sodium (mEq/l)		
• <125	0	0.0
• 125-130	17	41.5
• 131-135	10	24.4
• >135	14	34.1
Potassium (mEq/l)		
• <3.5	5	12.2
• 3.5-5.5	36	87.8
• >5.5	0	0.0

Table - 2: HE distribution of patients studied.

HE	No. of patients	%
No	30	73.2
Yes	11	26.8
Total	41	100.0

Table - 3: Ammonia distribution of patients studied.

Ammonia	No. of patients	%
Nil	30	73.2
High	11	26.8
Total	41	100.0

Table - 4: Clinical features in relation to HE of patients studied.

Clinical features	HE		Total (n=41)	P value
	No (n=30)	Yes (n=11)		
Ascites	27(90%)	11(100%)	38(92.7%)	0.551
Jaundice	22(73.3%)	7(63.6%)	29(70.7%)	0.701
Oedema	24(80%)	8(72.7%)	32(78%)	0.680
Bleeding	6(20%)	3(27.3%)	9(22%)	0.680
Pain	7(23.3%)	4(36.4%)	11(26.8%)	0.445
Alcohol	27(90%)	11(100%)	38(92.7%)	0.551

Table - 5: CHILDS distribution in relation to HE of patients studied.

CHILDS	HE		Total
	No	Yes	
Nil	1(3.3%)	0(0%)	1(2.4%)
A	15(50%)	1(9.1%)	16(39%)
B	14(46.7%)	5(45.5%)	19(46.3%)
C	0(0%)	5(45.5%)	5(12.2%)
Total	30(100%)	11(100%)	41(100%)

Table - 6: Comparison of Sodium and Potassium levels according to MELD of patients studied.

variables	MELD				Total	P value
	1-9%	10-19%	20-29%	30-39%		
Sodium (mEq/l)	133.00±7.07	135.73±4.52	131.81±3.54	127.57±1.51	132.20±4.50	0.001**
Potassium (mEq/l)	4.60±0.00	4.27±0.45	4.05±0.52	3.81±0.54	4.10±0.52	0.142

Discussion

Hyponatremia is a common finding in patients with decompensated cirrhosis due to an abnormal regulation of body fluid homeostasis. Although hyponatremia in cirrhosis was described more than 50 years ago, its importance in the clinical assessment of patients with cirrhosis was overlooked for many years. In current study, frequency of mild to moderate hyponatremia together in cirrhotic patients was observed 65% of patients. We also observed in our study patients with clinical features of hepatic

encephalopathy had elevated ammonia levels and also had low mean serum sodium levels. We also observed, patients with hyponatremia had high MELD score and child's grading of B and C. This suggested that hyponatremia can acts as precipitating factor for worsening of hepatic encephalopathy in cirrhotic patients and also marker of poor prognosis in those patients. In patients with cirrhosis, hyponatremia impairs quality of life because patients require a restriction of daily fluid intake to prevent further reductions in serum sodium concentration, and this is usually poorly tolerated. Treatment with vaptans represents a novel approach to improving serum sodium concentration in cirrhosis [12]. The short-term treatment with vaptans is associated with a marked increase in renal solute–free water excretion and improvement of hyponatremia. Long-term administration of vaptans seems to be effective in maintaining the improvement of serum sodium concentration. In a study done by Munaza Javid, et al., hyponatremia was observed in 72% of patients out of 132 patients [13]. In a study done by Jong Hoon Kim, et al., out of 188 patients with cirrhosis, nearly 56% of patients had different grades of hyponatremia [14]. There are lack of studies to correlate between hyponatremia and hyper ammonemia. In our study, we have found along with elevated serum ammonia levels there was evidence of hyponatremia, and lower mean serum sodium levels with high MELD score in patients with hepatic encephalopathy.

Table - 7: Sodium, Potassium and Ammonia levels according to MELD score.

variables	MELD				Total (n=41)	P value
	1-9% (n=2)	10-19% (n=11)	20-29% (n=21)	30-39% (n=7)		
Sodium (mEq/l)						
• <125	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	<0.001**
• 125-130	1(50%)	1(9.1%)	8(38.1%)	7(100%)	17(41.5%)	
• 131-135	0(0%)	2(18.2%)	8(38.1%)	0(0%)	10(24.4%)	
• >135	1(50%)	8(72.7%)	5(23.8%)	0(0%)	14(34.1%)	
Potassium (mEq/l)						
• <3.5	0(0%)	0(0%)	4(19%)	1(14.3%)	5(12.2%)	0.505
• 3.5-5.5	2(100%)	11(100%)	17(81%)	6(85.7%)	36(87.8%)	
• >5.5	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	
Ammonia						
• Nil	2(100%)	11(100%)	16(76.2%)	1(14.3%)	30(73.2%)	<0.001**
• High	0(0%)	0(0%)	5(23.8%)	6(85.7%)	11(26.8%)	

Conclusion

Since hyponatremia is common electrolyte abnormality which known to be overlooked and under treated. Clinicians should extremely careful while investigating a case of cirrhosis of liver and give priority to electrolyte imbalance, treatment of same. Significant efforts are required to optimize clinical management approaches in patients with cirrhosis of liver. Increased mortality can occur due to suboptimal therapy of these patients. Sustained resolution of hyponatremia is often difficult to achieve. V2 receptor blockade by Vaptans is certainly

effective, but their long-term safety, especially when associated to diuretics given to control ascites, has not been established as yet. As in other conditions, a rapid correction of long-standing hyponatremia can lead to irreversible brain damage. Its extremely important for all primary care physicians to recognize and also treat hyponatremia and hepatic encephalopathy.

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