Original Article

Frequency of hyponatraemia and its influence on liver cirrhosis-related complications

Samiullah Shaikh, Gomo mal, Shaikh Khalid, Ghulam Hussain Baloch, Yousfani Akbar
Department of Medicine, Liaquat University of Medical & Health Sciences, Jamshoro, Hyderabad.

Abstract

Objective: To evaluate the frequency, clinical associations and prognostic impact of hyponatraemia on cirrhosis related complications in patients with cirrhosis of liver.

Methods: In this case control study 217 cirrhotic patients consecutively admitted to our department from September 2006 to November 2007were studied. Serum sodium levels were determined in all patients admitted. The cutoff level of 130 meq/l was chosen because it is widely accepted to define hyponatraemia in patients with cirrhosis while the level of 135 meq/L is the lower normal value. Patients were grouped on the basis of serum sodium concentration into (1) serum sodium <130 meq/L (Group1) (2) serum sodium between 131 - 135 meq /l (Group 2), and (3) serum sodium >135 meq /l (Group3). P values of less than 0.05 were considered as significant. The patients with hyponatraemia Group1(<130 meq/l) and group 2 (131-135meq/l) were compared with group 3 (>135 meq/l) for the severity of liver disease, degree of ascites and other cirrhosis related complications such as hepatorenal syndrome, spontaneous bacterial peritonitis and hepatic encephalopathy.

Results: This case control study constituted 217 consecutive cirrhotic patients of which 141(65%) were male and 76/217 (35%) were female. Hyponatraemia (sodium <130meq/l) was found in 58 / 217 (26.7%) patients and 54/217 (24.9%) had serum sodium from 131-135meq/l whereas 105/ 217 (48.4%) patients had serum sodium >135. Out of 58 patients with hyponatraemia, 48 were in child -Pugh C class (p=0.001). Patients with serum sodium <130meq/l had more severe ascites (p= 0.001) requiring frequent paracentesis and higher dosages of diuretics. Hepatic encephalopathy was more frequent in patients with serum sodium < 130 meq/l (p= 0.001). The cirrhosis related complications were also significantly increased in patients with mild hyponatraemia (131-135 meq/l) than in patients with normal serum sodium (>135 meq/l).

Conclusion: Hyponatraemia is frequent in cirrhotic patients. It is seldom spontaneous and has a negative influence on cirrhosis related complications (JPMA 60:116; 2010).

Introduction

Hyponatraemia is frequent in cirrhosis with ascites. In a series by Arroyo et. al.[1] of their 50 consecutive cirrhotic patients in a year, 20 were found to have plasma Na below 130 meq/l. The hyponatraemia is thought to be due to a higher rate of renal retention of water in relation to sodium due to a reduction in solute-free water clearance. The consequent inability to adjust the amount of water excreted in the urine to the amount of water ingested leads to dilutional hyponatraemia.[2] The incidence of dilutional hyponatraemia in cirrhotic patients being treated for an episode of ascites is 35%, and it is one of the most important prognostic factors in these patients.[3] Patients with hyponatraemia have a poor survival compared with that of patients without hyponatraemia.[4] In contrast with the large amount of information that has been accumulated on the value of serum sodium in the prediction of prognosis, little is known regarding the clinical significance of the presence of hyponatraemia, particularly the relationship between serum sodium levels and characteristics of ascites and development

of complications of cirrhosis. Therefore, the aim of the present study was to assess the frequency of low serum sodium levels and to compare hyponatremic cirrhotic patients with normal sodium cirrhotic patients so as to assess the severity of liver disease, characteristics of ascites and occurrence of complications of cirrhosis such as hepatorenal syndrome (HRS) and spontaneous bacterial peritonitis (SBP) during hospital stay of the cirrhotic patients.

Methods

This case control study included 217 consecutive patients with cirrhosis of liver having ascites admitted in medical department of Liaquat university hospital Jamshoro/Hyderabad from September 2006 to November 2007. The recording of consecutive patients was designed to avoid any bias due to selection of patients. Patients were included in the study according to the following criteria: (1) diagnosis of cirrhosis confirmed clinical, biochemical, and ultrasonographic findings; and (2) presence of ascites determined via paracentesis or ultrasonography. The exclusion criteria were patients with hepatocellular carcinoma (HCC) and patients with exudative ascites.

The data of the patients was collected in a well designed proforma. The patients' demographics and the status of the patients at the time of inclusion (inpatient or outpatient) as well as severity of cirrhosis was assessed according to Child-Pugh score.[5] A total score from 5-6, 7-9 and 10-15 was classified as class A, B and C respectively. The patients were assessed for ascites and were graded according to International AscitesClub.[1,6]

1. Uncomplicated ascites: Ascites that is not infected and is not associated to hepatorenal syndrome. It is divided into 3 groups:

a. Grade 1 (mild): Only detected on ultrasound examination.

b. Grade 2 (moderate): Manifested by symmetric distention of the abdomen.

c. Grade 3 (severe): Gross ascites with marked abdominal distention.

2. Refractory ascites: It was defined in 1996 by the International Ascites Club as ascites that cannot be mobilized or the early recurrence of which (i.e., after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. Two subgroups were identified:

a. Diuretic-resistant ascites: Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of lack of response to dietary sodium restriction and intensive diuretic treatment.

b. Diuretic-intractable ascites: Ascites that cannot be removed (or the early recurrence of which cannot be prevented) because of complications induced by diuretics that preclude the administration of effective doses.

All patients were admitted for four week duration. During that period patients were assessed for the occurrence of complications of cirrhosis other than ascites, such as spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome.

The presence of portal-systemic encephalopathy (PSE) was diagnosed on the basis of speech, personality, intellectual disorders, and asterixis and graded as absent, mild or severe.[7] HCC was diagnosed by ultrasonography (US) or computed tomography (CT) imaging and high values of serum α-fetoprotein (>200 ng/ml) or by biopsy.

Patients were diagnosed to have hepatorenal syndrome according to International Ascites Club's definition of hepato-renal syndrome.[8]

1. Chronic liver disease with advanced hepatic failure and portal hypertension.

2. Low glomerular filtration rate, as indicated by serum creatinine of more than 1.5 mg/ dl or 24-hour creatinine clearance less than 40 ml /min.

3. Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhoea) or renal fluid losses (weight loss more than 500 g per day for several days in patients with ascites without peripheral oedema or 1,000 g per day in patients with peripheral oedema).

4. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg /dl or less, or increase in creatinine clearance to 40 ml/ minor more) after diuretic withdrawal and expansion of plasma volume with 1.5 litres of isotonic saline

5. Proteinuria less than 500 mg/dl and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

Patients with hepatorenal syndrome were given Terlipressin and albumin until the reversal of the HRS (decrease of serum creatinine below 1.5 mg/dl).[9]

SBP is the infection of the ascitic fluid that occurs in the absence of a visceral perforation and in the absence of an intra abdominal inflammatory focus such as abscess, acute pancreatitis or cholecystitis.[10] For SBP diagnosis, the number of polymorphonuclear leucocytes (PMN) from the ascitic fluid obtained by paracentesis, must exceed 250 cells/mm and or positive bacteriological cultures showing single organism. All patients with bacterial infection were submitted to treatment with cefotaxime or other antibiotics according to the results of cultures.

The patients on diuretic treatment were then classified

according to the number of diuretics that they were taking. The following information was then collected in patients on current diuretic treatment: dose of spironolactone (mg/d), furosemide (mg/d), and other diuretic agents. The following information on therapeutic paracentesis was collected: repeated use of paracentesis, time interval between the last two paracentesis (weeks), and volume of ascites removed at the last paracentesis (in liters).[10]

During hospital stay the dietary sodium was restricted to 50 meq per day for patients with ascites. In patients with mild hyponatraemia, the water intake was restricted to 750 ml/day and in those with severe hyponatraemia to 500 ml/day.

The tests carried out in the patients were serum electrolytes, serum creatinine, LFT, serum albumin, prothrombin time and were added in the proforma. Serum sodium was determined on admission and repeated weekly during the course of the patient. Patients were divided into three groups according to serum sodium concentration as follows: serum sodium <130 meql/l (Group1), serum sodium between 131 meq/l and 135 meq/l(Group 2), and serum sodium >135 meq/l (Group3). Group 3 was taken as control.Group1(<130 meq/l) and group 2 (131-135meq/l) were compared with group3 (>135 meq/l) for the severity of liver disease, degree of ascites and other cirrhosis related complications such as hepatorenal syndrome, spontaneous bacterial peritonitis and hepatic encephalopathy.

Statistics:

Descriptive statistics are provided as means ± 1 SD. The t-test was used to compare quantitative data, and the chi-square test was used for categorical data. All analyses were carried out using SPSS software version 16 (SPSS, Inc, Chicago,

P values of less than 0.05 were considered statistically significant. To determine the sample size, we assumed a confidence level of 95%, with a power of 80%. We predicted a finding of 30% hyponatraemia in our group of cirrhotic patients, on the basis of previous data.[11]

Results

This case control study framed 217 consecutive cirrhotic patients of which 141 (65%) were male and 76 (35%) female. The mean age of the patients were 46.8 ± 13 years. Hyponatraemia (sodium <130meq/l) was present in 58/ 217(26.7%) patients and 54/ 217 (24.9%) patients had serum sodium from 131-135 meq/l while 105/ 217 (48.4%) patients had serum sodium >135 meq/l. Patients with serum sodium < 130 meq/l were kept in group 1, with 131-135 meq/l in group 2 and >135 meq/l as control (group3). Table-1 shows basic characteristics of all the patients in the study. Low serum sodium had significantly high Child Pugh class compared to a normal serum sodium. Among 58 patients with serum sodium < 130 meq/l, 48 were in class C Child-Pugh and 10 were in Class B (p=0.001). A more severe grade of ascites was present in patients with low serum sodium. Grade 2 ascites was present in 12/58, grade3 in 33/58 patients and refractory ascites in 13/58 patients with serum sodium < 135 meq/l (p= 0.003) needing frequent paracentesis and higher dosages of diuretics. The duration of hospital stay of the patients was 3-5 weeks in all groups. During the hospital follow up of the patient 8/ 13 patients with refractory ascites developed hepatorenal syndrome with serum sodium <130

Table-1: Baseline Characteristics of patients with cirrhosis of liver admitted at Liaquat University Hospital, Jamshoro, Hyderabad.

Variables	Number of patients	Frequency	Percent
Sex Male	217	141	65
Female		76	35
Ascites		-	-
Grade2(moderate)	217	82	37.8
Grade3(severe)		116	53.5
Refractory ascites		19	8.7
H/Diabetes Mellitus	217	-	
Yes	192	88.5	
No	25	11.5	
Ch.Pugh grade*	217	-	-
Grade-B	84	38.5	
Grade-C	133	61.5	
S.sodium level(meq/l)	217		
<130	58	26.7	
131-135	54	24.9	
>135	105	48.4	
Paracentesis	217	-	-
No paracentesis		88	40.6
Paracentesis once		60	27.6
Paracentesis twice		30	13.8
Paracentesis >twice		39	18
H/O Diuretics**	217	197	88.9
No H/O Diuretics		20	10.1
Spironolactone		197	88.9
Spironolactone and furosemide		167	76.9

*Ch.Pugh grade: Child Pugh Score. ** H/O Diuretics: History of Diuretics.

Table-2: Comparison of liver cirrhosis related complications according to serum sodium levels.

Parameter	S.Sodium <130meq/l (n=58) group1	S.Sodium <131-135meq/l (n=54) group2	S.Sodium >135meq/l (n=105) group3
Child-Pugh Class			
B	10	17	64
C	48	35	41
P=Value	0.001	0.002	0.144
Encephalopathy			
No	43	49	98
Yes	15	06	7
P=Value	0.001	0.005	0.40 (NS)
Ascites	12	15	40
Grade2	33	37	58
Grade3	13	2	7
Refractory	0.001	0.029	0.87(NS)

meq/l and one patient with serum sodium 130-135 meq/l. Spontaneous bacterial peritonitis was present in 10/58 patients with serum sodium < 130 meq/l ,3/54 patient with serum sodium 131-135 meq/l and 1/105 patient with >135 meq/l. Hepatic encephalopathy was present in 26/217 (11.9%) patients, of which15/58(25.8%) patients were with serum sodium <130meq/l (p=0.001). Table-2 shows the comparison of cirrhosis related complications according to serum sodium. History of diuretic therapy was present in 193/217 (88.9%).All patients were on Spironolactone ranging from 100-300mg/d and 167/217 (76.9%) patients were on combination of Spironolactone and furosemide given in a dosage of 12 to 40 mg/d. Large volume paracentesis was done once or more in 30/217 (13.7%) patients.

Discussion

This case control study was done for assessing serum sodium concentration in patients with cirrhosis and the association between serum sodium levels and the occurrence of major complications of cirrhosis. The results indicate that a large proportion of patients with cirrhosis have abnormal values of serum sodium concentration. In fact, more than one half (51.6%) of patients with cirrhosis had values of serum sodium concentration below the normal range (<135 meq/l) and 58/217 (26.7%) had values <130 meq/l. Low serum sodium levels were more frequent in patients with severe liver failure (59.9% (Child-Pugh class C) irrespective of age and sex of the patients. Nevertheless, it should be pointed out that low serum sodium levels were also found in patients with moderate liver failure (Child-Pugh B). The frequency of serum sodium <130 mmol/L was 26.7% in our patients in accordance with a study by Borroni G et al where hyponatraemia was present in 30% of cases.[12] Arroyo et al. also found hyponatraemia < 130 in 30% of cases.[13] Moreover, our study showed that the occurrence of low serum sodium levels is greater than previously reported, because a further 24.9% of patients had a mild reduction in serum sodium levels (between 131 and 135 meq/l).Although, it is generally believed that the existence of a serum sodium concentration <130 meq/l is associated with difficult-to-treat ascites, few studies have been reported that specifically analyze the relationship between serum sodium levels and responsiveness of ascites to diuretic therapy. Arroyo et al.[13] reported that the presence of serum sodium <130 meq/l was associated with lower glomerular filtration rate and solute-free clearance and a poorer response to diuretics compared with patients with serum sodium>130 meq/l. Subsequent study by Bernardi et al.[14] showed that patients who do not respond to diuretics have lower serum sodium concentration compared with patients who respond to diuretics. The results of the current study 46/58 (79%) confirm and extend these observations by showing that patients with serum sodium concentration <130 meq/l have a higher frequency of refractory ascites, lower response in terms of change in body weight, higher requirement of large-volume paracentesis to manage their ascites, and a shorter interval between paracentesis.

Subsequent study by Bernardi et al.[14] and Angeli[15] showed that patients who do not respond to diuretics have lower serum sodium concentration compared with patients who respond to diuretics Moreover, the results show that patients with serum sodium between 131 and 135 meq/L 28/54 (53.7%) have signs of poor ascites response compared with patients with normal serum sodium concentration (34/105) (32%), although to a lesser extent than patients meeting the classical definition of hyponatraemia (serum sodium <130 meq/l). Hepatorenal syndrome was also strongly associated with low serum sodium concentration as 8/13 patients with refractory ascites with serum sodium <130 meq/l developed hepatorenal syndrome during follow up as compared to one patient with serum sodium 130-135 meq/l and none with normal serum sodium concentration .This association may be explained by the fact that hepatorenal syndrome is frequently associated with an impaired excretion of solute-free water, so that the majority of patients with hepatorenal syndrome have a concomitant reduction of serum sodium concentration.[16,17] Alternatively, it has been shown that hyponatraemia is a major risk factor for the development of hepatorenal syndrome in patients with ascites. This increased risk of hepatorenal syndrome may be related to a more severe circulatory dysfunction of patients with hyponatraemia compared to patients without hyponatraemia.[3] Our data also indicate the existence of an association between spontaneous bacterial peritonitis and low serum sodium levels in accordance with another study done by Paolo Angeli et al.[15] This association probably reflects the impairment in effective circulating blood volume that occurs in patients with cirrhosis in the setting of spontaneous bacterial peritonitis and may lead to hepatorenal syndrome in some patients, while others may develop only hyponatraemia.[18]

In fact, the frequency of hepatic encephalopathy was associated with serum sodium levels in such a way that patients with serum sodium <130 meq/l had a significantly greater frequency 15/58(25.8%) of hepatic encephalopathy compared to patients with normal serum sodium concentration 9/92 (9.7%). Patients with serum sodium between 131 and 135 meq/l had a lower frequency of encephalopathy 06/52 (11.2%) compared to patients with serum sodium <130 meq/l, but higher than that of patients with normal serum sodium concentration. According to Paolo Angeli[15] encephalopathy was present in 38% of the patients with serum sodium <130 meq/l compared with 24% of patients with serum sodium between 131 and 135 meq/l and 15% of patients had serum sodium levels >135 meq/l. The relationship between hepatic encephalopathy and serum levels may be explained on the

basis of more severe liver failure among patients with serum sodium <130 meq/l, and the possibility that the two events may be pathophysiologically linked.[15] In fact, it has been demonstrated that low serum sodium levels in patients with cirrhosis are associated with a remarkable reduction in the cerebral concentration of organic osmolytes that probably reflect compensatory osmoregulatory mechanisms against cell swelling triggered by a combination of high intracellular glutamine, as a consequence of hyperammonemia, and low extracellular sodium.[19-21] In experimental models of acute liver failure, the presence of hyponatraemia is associated with larger brain swelling compared with normal serum sodium concentration.[22] Although the results do not make it possible to prove the existence of a causal link between low serum sodium levels and these three major complications of cirrhosis, they suggest the possibility of a potentially negative impact of low serum sodium levels and even a mild reduction in the clinical course of cirrhosis. Moreover, the results suggest that serum sodium levels should be closely monitored in patients experiencing these complications. These findings indicate that close monitoring of serum sodium concentration should be performed in patients with cirrhosis throughout the course of the disease in order to prevent the rapid development of cirrhosis related complications.

Conclusion

In conclusion, the results of this study indicate that low serum sodium levels are a common feature in patients with cirrhosis. The existence of serum sodium concentration <135 meq/l-is associated with a poor control of ascites requiring either larger dosages of diuretics or repeated paracentesis and greater frequency of hepatic encephalopathy compared with patients with serum sodium concentration within the normal range (>135 meq/l). Patients with a serum sodium concentration <130 meq/l are those with the greatest frequency of severe ascites and associated complications. Nevertheless, even patients with a mild reduction in serum sodium concentration should be considered a high-risk population because of their more severe ascites and greater frequency of major complications of cirrhosis compared with patients with normal serum sodium concentration.

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