Evaluation of hyponatremia among cirrhotic patients in Shariati Hospital, Isfahan, Iran

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Introduction: Patients with advanced cirrhosis are susceptible to hyponatremia due to impaired kidney function. Recent studies have shown that hyponatremia can be an independent predictor of hepatic encephalopathy (HE) in these patients.

Aim: The present study performed to evaluate the relationship between serum sodium concentration and HE in patients with cirrhosis.

Material and methods: This cross-sectional study was conducted on 65 cirrhotic patients admitted to the internal ward of Shariati Hospital in Esfahan, Iran. Patients were divided into two groups based on serum sodium concentration: (1) hyponatremic patients with serum sodium less than 135 meq/L and (2) those with serum sodium not less than 135 meq/L. Groups were compared regarding demographic characteristics, causes of cirrhosis, diuretics consumption, prevalence of HE, and severity of cirrhosis assessed using MELD and Child–Pugh scores, as well as biochemical measurements.

Results: Based on serum sodium levels, 21 patients (32.3%) had hyponatremia. Thirty (46.2%) individuals had HE. Comparing hyponatremic patients with those without low serum sodium, there were no statistically significant differences in gender, causes of cirrhosis, and MELD score between groups ($P > 0.05$); however, hyponatremic patients had more prevalence of HE ($P < 0.001$), diuretic intake ($P < 0.001$), lower levels of albumin ($P = 0.003$), and were older ($P = 0.017$). Severity of cirrhosis in patients with hyponatremia was mostly in groups B and C of Child–Pugh ($P = 0.002$).

Discussion: In summary, HE is frequent in cirrhotic patients with hyponatremia.

Conclusions: It is suggested to monitor serum sodium level in patients with cirrhosis to prevent HE and other complications, especially among those who are taking diuretics.
1. INTRODUCTION

Advanced cirrhosis results in hyponatremia that is reported in nearly 57% of cirrhotic patients. In cirrhosis, hyponatremia may occur due to either hypovolemia or hypervolemia; however, the former, dilutional hyponatremia is more common. The development of dilutional hyponatremia in patients with cirrhosis is multi-factorial. Systemic vasodilation because of nitric oxide (NO) synthesis, release of antidiuretic hormone (ADH), and activation of renin-angiotensin-aldosterone and sympathetic nervous system are involved. Hyponatremia may enhance the risk of early mortality and complications like infection, renal failure, and encephalopathy.

Severity of cirrhosis is assessed by the Model for End-stage Liver Disease (MELD) scores. Some researchers have suggested incorporating serum sodium into the MELD score to make a more accurate survival prediction following liver transplantation. Hazard ratio (HR) of risk adjusted mortality at 90 days in hyponatremic patients undergoing transplant have been found to be higher compared with controls with normal sodium levels.

Hepatic encephalopathy (HE) is a complication of liver cirrhosis that can occur in about 70%–50% of patients with cirrhosis and is significantly associated with morbidity and mortality rates, as well as poor health-related quality of life (HRQOL). Several factors other than hyperammonemia have been suggested to play a role in the development of HE such as manganese, hyponatremia, and inflammation. Some studies have shown hyponatremia as a predictive factor for the development of HE. Additionally, in patients with minimal HE, hyponatremia can be indicative of resistant to treatment with lactulose. However, there are few studies that have been conducted to explore possible association between hyponatremia and development of HE in cirrhotic patients.

2. AIM

The aim of this study was to assess the relationship between serum sodium levels and the prevalence of HE in cirrhotic patients.

3. MATERIAL AND METHODS

To determine the sample size, we assumed a confidence level of 95%, with a power of 80%. Based on previous data, we considered a prevalence of 20% for hyponatremia in our cirrhotic patients and a total of 62 participants were obtained. The study was involved 65 patients diagnosed with cirrhosis based on clinical, biochemical, and morphological criteria. The study was performed in the Internal Clinic of the Shariati Hospital of Isfahan, Iran, from September 2015 and November 2016. The protocol of study was approved by the Ethics Committee of the Najafabad Islamic Azad University. Written informed consent was provided by all patients before study entry. Subjects with neurological disorders, stroke, concussion, history of transjugular intrahepatic portosystemic shunt, neoplasms, cardiovascular diseases, inflammatory or infectious diseases, use of sedative drugs, supplements or medications containing sodium, fever, and shock were excluded.

Demographic, clinical, and biochemical data were obtained from patients. Causes of cirrhosis – cryptogenic, hepatitis C virus (HCV), hepatitis B virus (HBV), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH) – were defined. The patients on diuretic treatment were asked to describe duration of therapy.

Serum sodium was measured and hyponatremia was defined as serum sodium concentration less than 135 mEq/L. Disease severity scores model for end stage liver disease (MELD) was calculated from serum creatinine (mg/dL), serum bilirubin (mg/dL) and prothrombin time (INR) according to the UNOS guidelines. Child–Pugh score was also calculated to evaluate the stage of liver cirrhosis. Accordingly, patients were assigned to one of three groups: stage A, stage B, and stage C.

Results were analyzed using SPSS (2013 IBM SPSS Statistics for Windows, v. 22.0). Categorical variables were analyzed using χ² and quantitative continuous data were compared using Student’s t test. Whenever data were not normally distributed, we used logarithmic transformation. Otherwise, nonparametric statistics were used. A P value of less than 0.05 was considered to be statistically significant.

4. RESULTS

Mean age of patients was 58.4 ± 14.8 years. Thirty-six (55.4%) participants were males and 29 (44.6%) were females. Most common etiological factors order of frequency were cryptogenic, HCV, HBV, PSC and AIH. Mean MELD score was 13.4

Table 1. Demographic characteristics (n = 65).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) mean ± SD</td>
<td>58.4 ± 14.8</td>
</tr>
<tr>
<td>Sex, n(%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36(55.4)</td>
</tr>
<tr>
<td>Female</td>
<td>29(44.6)</td>
</tr>
<tr>
<td>Cirrhosis causes, n(%)</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>40(61.5)</td>
</tr>
<tr>
<td>HBV</td>
<td>7(10.8)</td>
</tr>
<tr>
<td>HCV</td>
<td>11(16.9)</td>
</tr>
<tr>
<td>PSC</td>
<td>2(3.1)</td>
</tr>
<tr>
<td>AIH</td>
<td>2(3.1)</td>
</tr>
<tr>
<td>Others</td>
<td>3(4.6)</td>
</tr>
<tr>
<td>MELD score, mean ± SD</td>
<td>13.4 ± 8.7</td>
</tr>
<tr>
<td>Serum sodium (mEq/L), mean ± SD</td>
<td>136.3 ± 5.0</td>
</tr>
<tr>
<td>Child Pugh, n(%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>26(40.0)</td>
</tr>
<tr>
<td>B</td>
<td>23(35.4)</td>
</tr>
<tr>
<td>C</td>
<td>16(24.6)</td>
</tr>
<tr>
<td>Diuretic intake, n(%)</td>
<td></td>
</tr>
<tr>
<td>Spironolakton</td>
<td>20(30.8)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>6(9.2)</td>
</tr>
<tr>
<td>Diuretic intake duration (m), mean ± SD</td>
<td>12.8 ± 7.8</td>
</tr>
<tr>
<td>HE, n(%)</td>
<td>30(46.2)</td>
</tr>
<tr>
<td>Ascites, n(%)</td>
<td>65(100)</td>
</tr>
<tr>
<td>Hyponatremia, n(%)</td>
<td>21(32.3)</td>
</tr>
</tbody>
</table>
± 8.7 and most patients (40%) were in class A of Child–Pugh. Based on serum sodium levels, 21 patients (32.3%) had hyponatremia. Thirty (46.2%) individuals had HE (Table 1). Comparing hyponatremic patients with those without low serum sodium, there were no statistically significant differences in gender, causes of cirrhosis, MELD score, and some biochemical measurements (ALT, AST, ALP, total bilirubin, creatinine, INR) between groups ($P > 0.05$); however, hyponatremic patients had more prevalence of HE ($P < 0.001$), diuretic intake ($P < 0.001$), lower levels of albumin ($P = 0.003$), and were older ($P = 0.017$). Severity of cirrhosis in patients with hyponatremia was mostly in groups B and C of Child–Pugh ($P = 0.002$) (Table 2).

Table 2. Biochemical variables in the groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum sodium $&lt; 135$ mEq/L ($n = 21$)</th>
<th>Serum sodium $\geq 135$ mEq/L ($n = 44$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>64.7 ± 12.1</td>
<td>55.4 ± 15.2</td>
<td>0.017</td>
</tr>
<tr>
<td>MELD score, mean ± SD</td>
<td>15.8 ± 8.0</td>
<td>12.3 ± 8.8</td>
<td>0.133</td>
</tr>
<tr>
<td>Sex, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12(57.1)</td>
<td>24(54.5)</td>
<td>0.844</td>
</tr>
<tr>
<td>Female</td>
<td>9(42.9)</td>
<td>20(45.5)</td>
<td></td>
</tr>
<tr>
<td>HE, n(%)</td>
<td>19(90.5)</td>
<td>11(25.0)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Diuretic intake, n(%)</td>
<td>15(71.4)</td>
<td>11(25.0)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Cryptogenic, n(%)</td>
<td>12(57.1)</td>
<td>28(63.6)</td>
<td>0.615</td>
</tr>
<tr>
<td>HBV, n(%)</td>
<td>1(4.8)</td>
<td>6(13.6)</td>
<td>0.280</td>
</tr>
<tr>
<td>HCV, n(%)</td>
<td>6(28.6)</td>
<td>5(11.4)</td>
<td>0.084</td>
</tr>
<tr>
<td>PSC, n(%)</td>
<td>0(0)</td>
<td>2(4.5)</td>
<td>0.321</td>
</tr>
<tr>
<td>AIH, n(%)</td>
<td>0(0)</td>
<td>2(4.5)</td>
<td>0.321</td>
</tr>
<tr>
<td>Others, n(%)</td>
<td>1(4.8)</td>
<td>2(4.5)</td>
<td>0.969</td>
</tr>
<tr>
<td>Child pugh, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>2(9.5)</td>
<td>24(54.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>B</td>
<td>11(52.4)</td>
<td>12(27.3)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>8(38.1)</td>
<td>8(18.2)</td>
<td></td>
</tr>
<tr>
<td>ALT (U/L), median(IQR)</td>
<td>52.5(26.0–117.0)</td>
<td>44.5(23.5–64.0)</td>
<td>0.303</td>
</tr>
<tr>
<td>*AST (U/L), mean ± SD</td>
<td>72.3 ± 2.2</td>
<td>49.0 ± 2.6</td>
<td>0.123</td>
</tr>
<tr>
<td>*ALP (U/L), mean ± SD</td>
<td>285.2 ± 1.5</td>
<td>291.5 ± 1.7</td>
<td>0.875</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL), median(IQR)</td>
<td>1.6(1.2–3.5)</td>
<td>1.4(0.9–2.2)</td>
<td>0.078</td>
</tr>
<tr>
<td>Albumin (g/dL), median(IQR)</td>
<td>2.7(2.2–3.3)</td>
<td>3.6(2.7–4.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine (mg/dL), mean ± SD</td>
<td>1.47 ± 0.04</td>
<td>1.02 ± 0.32</td>
<td>0.283</td>
</tr>
<tr>
<td>INR, median(IQR)</td>
<td>1.4(1.1–1.8)</td>
<td>1.1(1.0–1.5)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Comments: * Data are transformed to logarithm.

5. DISCUSSION

Low serum sodium is related to poor prognosis, increased risk of mortality, infection, renal failure, and encephalopathy in patients with advanced liver diseases.4 In total of cirrhotic patients participating in the present study 32.3% had hyponatremia that represents the high prevalence of this electrolytic disorder among patients with cirrhosis. Barakat et al. estimated the prevalence of hyponatremia at 59.46% in cirrhotic patients,14 while the estimated prevalence rate of hyponatremia were 24.3% and 50.54% in other studies.15,16 The difference in the prevalence of hyponatremia in cirrhotic patients could be explained by differences in sample size, cut-point used for defining hyponatremia, and severity of cirrhosis in patients. Hyponatremia has been related to increased severity of liver disease based on the MELD score.17 We could not find this relationship; maybe because both groups of patients had similar values of bilirubin, INR, and creatinine.

Complications such as severe ascites, impaired kidney function, spontaneous bacterial peritonitis, HE, and hepatorenal syndrome have been reported to be more common in cirrhotic-hyponatremic patients in a large cross-sectional study.1 The prevalence of HE in our patients was 46.2%. This syndrome impairs quality of life and reduces life expectancy in cirrhotic patients, so it seems necessary to investigate factors associated with HE. Our study showed that 90.5% of cirrhotic patients with hyponatremia had HE which demonstrates high susceptibility of cirrhotic patients with hyponatremia to HE. Our results support findings of other studies. Shaikh and his colleagues reported higher frequency of HE in patients with serum sodium less than 130 meq/L compared to those with normal serum sodium concentration (25.8% vs. 9.7%, respectively).18 A negative relationship between serum sodium levels and frequency of HE has been shown in previous studies, especially in those with serum sodium less than or equal to 130 mmol/L.1 Change of cell hydration due to decreased extracellular sodium results in osmotic stress and astrocyte swelling; cells that are involved in the maintenance of central nervous system (CNS) function.19 Serum sodium less than or equal to 131 mmol/L has been demonstrated to be the best predictor of grade I of HE.20 In another study of patients with cirrhosis, serum sodium level was reported to be an independent predictor...
of electroencephalographic abnormalities. It has shown an association between serum sodium and HRQOL, cognition, and brain MR spectroscopy metabolites in patients with cirrhosis. Furthermore, presence of HE made their abnormalities worse. The underlying reason has been attributed to impaired functioning of CNS. These findings propose a possible potential negative role for low serum sodium concentration in cirrhosis-related complications. As patients with serum sodium levels above 120 meq/L are asymptomatic, regular serum sodium evaluating should be recommended in cirrhotic patients.

High rates of consumption of diuretics among our cirrhotic patients with hyponatremia show possible effects of diuretics on the risk of hyponatremia in HE. This finding is in line with Shaikh et al. Therefore, due to the probable negative impact of hyponatremia on complications such as encephalopathy, diuretics should be prescribed cautiously in cirrhotic patients.

Our findings indicate that mean age of cirrhotic patients with hyponatremia was more than cirrhotic patients without hyponatremia. This finding proposes this hypothesis that older cirrhotic patients are at greater risk of developing hyponatremia and should be screened periodically for hyponatremia (especially if they are on diuretics treatment). In other words, diuretics should be prescribed warily in older cirrhotic patients.

The cirrhosis grade of majority of patients in the present study (40%) was Child–Pugh A. This was Child-Pugh B in Iwasa’s study. However, most of our cirrhotic patients with hyponatremia (90.5%) had Child–Pugh B and C. This confirms a significant association between severity of cirrhosis and decreased serum sodium that has been reported in previous studies.

6. CONCLUSIONS

In conclusion, the findings of the current study reveal presence of HE in cirrhotic patients with hyponatremia. So, monitoring serum sodium level in patients with cirrhosis is prudent to prevent HE and other complications, especially among those who are taking diuretics.

Conflict of interest
None declared

Acknowledgement
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References
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