Dilutional Hyponatremia in Patients With Cirrhosis and Ascites

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Objectives: To analyze the predisposing factors, modifications of vasoactive systems, and prognosis of patients with cirrhosis and hyponatremia.

Patients and Methods: Fifty-four patients with hyponatremia (serum sodium level of <130 mEq/L after 5 days of hyponatremic diet and no diuretic therapy). Twenty cirrhotic patients served as controls. We measured plasma renin activity and levels of plasma aldosterone, norepinephrine, and antidiuretic hormone. Follow-up identified the development of hepatorenal syndrome and death.

Results: A higher percentage of patients with hyponatremia had decreased liver size, higher levels of plasma renin activity, and higher serum concentrations of aldosterone and norepinephrine. Renal insufficiency was detected in 31 of them (57%). Precipitating factors (hemorrhage or infections) were detected in 27 patients (50%). Incidence of hepatorenal syndrome and death were higher in patients with spontaneous development of hyponatremia (n=23 [85%] and n=25 [93%], respectively) than in patients with precipitating factors (n=15 [56%] and n=12 [44%], respectively) and cirrhotic controls (n=1 [5%] and n=5 [25%], respectively) (P<.001). Results of multivariate analysis showed that Child-Pugh index, presence of hepatocarcinoma, and serum concentration of urea were associated with mortality. After excluding those patients with kidney failure at the time of admission, only Child-Pugh index and norepinephrine concentrations were independent predictors of mortality.

Conclusions: Hyponatremia is an alteration in patients with advanced liver disease. Although survival is significantly reduced in patients with spontaneous development of hyponatremia, a reduced sodium concentration cannot be considered as an independent predictor of the risk for death.

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AN ACTIVATION of the renin-angiotensin-aldosterone system and the sympathetic nervous system and a nonosmotic release of vasopressin frequently develop in patients with cirrhosis. This sequence of events results in enhanced renal water and sodium reten-

tion, ascites, impaired free-water excretion, and, frequently, hepatorenal syndrome.¹,² Hepatorenal syndrome is characterized by a marked reduction in re-
nal blood flow and glomerular filtration rate in the absence of histological abnormalities in the kidney and other known causes of renal failure. It is associated with an ex-
tremely short survival.³ Decreased liver size, increased plasma renin activity (PRA), and dilutional hyponatremia have been considered predictors of hepatorenal syndrome in these patients.³,⁴ Precipitating factors of hepatorenal syndrome have been de-
scribed, eg, gastrointestinal tract hemorrhage or bacterial infections.⁵,⁶

Dilutional hyponatremia is considered to be the consequence of a higher rate of renal retention of water in relation to sodium, due to a decrease in free-water clearance.⁶ Although accepted as an intermediate event in the sequence that leads to hepatorenal syndrome, the incidence of hyponatremia in patients with cirrhosis has received little attention.⁷ Clinical or analytical data that could predict the development of hyponatremia and the course of patients with cirrhosis and hyponatremia are also unknown or only poorly analyzed in short series of cases.⁷-¹⁰

The present prospective study reports the results of a follow-up analysis in a series of cirrhotic patients with ascites. We investigated the incidence, precipitating factors, and prognosis of dilutional hyponatremia in these patients.

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PATIENTS AND METHODS

SAMPLE SIZE

To determine the sample size, we assumed a confidence level of 95%, with a power of 80%. We predicted a finding of 30% hyponatremia in the cirrhotic patients we attended, on the basis of previous data. Because the percentage of patients with precipitating factors of hepatorenal syndrome approached 50%, we predicted that half of the patients with hyponatremia had precipitating factors and that the other half were patients with spontaneously developed hyponatremia. Thus, the ratio of cirrhotic patients with hyponatremia to patients without hyponatremia was 1:2.

A minimum of 20 cirrhotic control subjects and 40 cirrhotic patients with hyponatremia (20 with hyponatremia preceded by precipitating factors and 20 with spontaneously developed hyponatremia) were therefore needed.

STUDY POPULATION

During a 6-month period, 155 patients were hospitalized for different complications of the cirrhosis of liver and ascites at the Digestive Diseases Unit of the Hospital Universitario Puerta del Mar, Cádiz, Spain. Fifty-four of them presented with dilutional hyponatremia, whereas the sodium concentration was within reference range in the remainder (n=101). Those patients with dilutional hyponatremia constituted our study population.

Dilutional hyponatremia was defined as a serum sodium level of lower than 130 mEq/L after 5 days of a diet containing 30 mEq/d of sodium, restricted water ingestion (<500 mL/d), and no diuretic therapy. Other known causes of hyponatremia (ie, digestive losses, salt-losing nephropathy, Addison disease, osmotic diuresis, postobstructive renal insufficiency, congestive heart failure, nephrotic syndrome, inappropriate antidiuretic hormone [ADH] secretion secondary to neoplasms, hypothyroidism, pulmonary diseases, or central nervous system diseases) were excluded by clinical and/or analytical methods. Primary causes of admission of these patients were digestive hemorrhage due to hypertensive gastropathy (n=4 [7%]) or esophageal varices (n=6 [11%]); ascites (n=8 [15%]); pleural effusion (n=2 [4%]), hepatorenal syndrome (n=4 [7%]); hepatic encephalopathy (n=11 [20%]); infectious diseases, including spontaneous bacterial peritonitis, primary bacteremia, and pneumonia (n=16 [30%]); and hepatocarcinoma (n=3 [6%]). Apart from these primary causes of admission, all patients with hyponatremia presented with ascites.

Twenty consecutive patients with cirrhosis and ascites were randomly selected as controls. Primary causes of admission of controls were digestive hemorrhage due to hypertensive gastropathy (n=3 [15%]) or esophageal varices (n=6 [30%]); ascites (n=7 [35%]); infectious diseases, including spontaneous bacterial peritonitis and pneumonia (n=3 [15%]); and hepatocarcinoma (n=1 [5%]). Characteristics of the study population are shown in Table 1.

Informed consent was obtained from each patient, and the study was approved by the Research and Ethics Committee of the hospital.

STUDY SCHEDULE AND MEASUREMENTS

After admission, a detailed history was obtained, and a physical examination was performed. Diuretic therapy was withdrawn in patients and controls. The causes of admission were initially treated only if they acutely compromised the liver (eg, digestive hemorrhage, liver encephalopathy and infections). After hemodynamic stabilization, patients were prescribed a diet that included sodium ingestion of 50 mEq/d and restricted water ingestion (<500 mL/d). On day 5, a 24-hour urine sample was collected to measure electrolyte concentration. On day 6, after overnight fasting, an antecubital vein was catheterized. Blood samples were obtained to measure serum levels of electrolytes, urea, and creatinine and to perform standard liver function tests. After 2 hours of bed rest, blood pressure was measured, and blood samples were collected in iced tubes containing EDTA and sodium azide. After centrifugation at 4°C, the plasma was immediately frozen at −30°C until assay for PRA and higher prevalence of ascites before the onset of the study, higher serum concentrations of urea, and a higher prevalence of decreased liver size. The causes of the cirrhosis and serum and urine concentrations of potassium were similar in patients and controls (Table 1).

The following precipitating factors were detected in 27 patients (50% of all patients with hyponatremia): infection in 17 patients (spontaneous bacterial peritonitis in 8, pneumonia in 5, and primary bacteremia in 4); digestive hemorrhage in 9 patients (variceal hemorrhage in 5 and hypertensive gastropathy in 4); and pneumonia plus hemorrhage due to hypertensive gastropathy in 1 patient. Twelve (44%) of these patients died as a result of the precipitating factors (infection in 7 patients, digestive hemorrhage in 4 patients, and infection and hemorrhage in 1 patient). Serum sodium concentrations returned to the reference range in the remaining 15 patients, who survived the precipitating factors. Hyponatremia persisted in the 27 patients in whom it developed spontaneously, in the absence of precipitating factors.
concentrations of plasma aldosterone (PAC), ADH, and nor-epinephrine (NE) using commercially available kits. Plasma renin activity was determined by means of radioimmunoas-
say (Clinical Assays; Baxter, Cambridge, Mass). Mass of generated angiotensin I after 30 minutes of incubation at a pH of 7.4 and 37°C, under conditions to inhibit further conversion of an-
giotensin I (reference range, 400-2300 pg/mL per hour [308.8-
1775.6 pmol/L per hour]). We measured levels of PAC (Al-
doctk-2-P2714; Sorin Biomedica Diagnostics, Barcelona, Spain; 
reference range, 3.3-15.0 ng/dl [0.08-0.42 nmol/L], ADH 
(Bühlman Laboratories, Basel, Switzerland; reference range, 
<1.0 pg/mL [<0.9 nmol/L], and NE (IBL Laboratories, Hamb-
burg, Germany; reference range, 150-370 pg/mL [0.9-2.2 nmol/ 
L]) by means of radioimmunoassay. Methods used for these 
investigations have been described in detail elsewhere.11-14

On day 6, time-motion, 2-dimensional, and Doppler abdo-
nal ultrasonographic examinations were per-
formed using an ultrasonoscope (Hitachi EUB-525; Hitac-
chi Medical Corp, Tokyo, Japan) with 2.5- and 3.5-MHz trans-
ducers. Liver size, determined by means of ultrason-
ography, was considered to be normal if the longitudinal 
diameter of the right liver lobe was 10 to 15 cm. The re-
sistive index of the renal arteries was calculated by the analy-
sis of Doppler signals obtained from arcuate arteries at the 
corticomedullary junction of the left kidney. The resistive 
index is defined by the following ratio15:

(Peak Systolic Frequency Shift−Minimum Diastolic 
Frequency Shift)/Peak Systolic Frequency Shift

Only 2 trained observers (P.R. and M.M.) performed the 
ultrasonographic studies, to avoid interobserver vari-
tions. Three individual sets of measurements were ob-
tained from each ultrasonographic study, and the results 
were averaged. The discrepancy between measurements was 
less than 10% in every case.

Precipitating factors of hyponatremia were consid-
ered when a complication of cirrhosis of liver, usually a com-
plication of portal hypertension, was chronologically re-
lated to hyponatremia.

Renal failure at the time of enrollment was diagnosed 
when the serum creatinine level was greater than 1.5 mg/dL.

(Significantly higher PRA and PAC levels were de-
tected in patients with hyponatremia with or without pre-
cipitating factors, compared with controls. In patients with 
hyponatremia without precipitating factors, signifi-
cantly higher concentrations of plasma NE were de-
tected than in controls. Plasma values of ADH were simi-
lar in all 3 groups (Table 2). The more enhanced 
concentrations of these hormones were detected in pa-
tients with renal insufficiency (data not shown).

Because renal failure could modify the results, a com-
parative analysis of patients without kidney failure and con-
trols was performed. Excluding those patients with renal 
insufficiency present at the time of admission, differential 
characteristics between hyponatremic (n=23) and nonhy-
ponatremic (n=13) subjects were maintained. Previous as-
cites was present in 20 patients (87%) vs 7 controls (54%) 
(P<.05). In a comparison of patients and controls, serum 
urea levels were 39±11 vs 29±11 mg/dL (P<.01); serum 
sodium levels, 123.7±3.8 vs 135.8±3.7 mEq/L (P<.001); 
urinary sodium levels, 5±3 vs 54±47 mEq/24 hours 
(P<.01); PRA, 11,000±5200 vs 4700±5700 pg/mL per hour 
(260.7±123.2 vs 111.4±135.1 pmol/L per hour) (P<.05); 
PAC levels, 86.5±22.0 vs 28.7±34.5 ng/dL (2.3±0.6 vs 
0.8±0.9 nmol/L) (P<.001); and renal resistive index, 
0.67±0.24 vs 0.63±0.20 (P=.03).

FOLLOW-UP

Hepatorenal syndrome developed in 1 cirrhotic control 
(5%), 15 patients with hyponatremia with precipitating 
factors (56%) (OR, 23.75 [95% CI, 2.76-1050.91]; P<.001 
vs cirrhotic controls), and 23 patients with hyponatre-
mia without precipitating factors (85%) (OR, 10.925 [95% 
CI, 10.10-4723.50]; P<.001 vs cirrhotic controls; and OR, 
4.60 [95% CI, 1.09-22.70]; P<.05 vs patients with pre-
cipitating factors). The cirrhotic control in whom hepa-

torenal syndrome developed presented with a serum so-
dium level of 130 mEq/L at the time of inclusion in the 
study. Hepatorenal syndrome did not develop in any pa-
tient with a serum sodium of greater than 130 mEq/L.
Death occurred in 5 cirrhotic controls (25%), 12 patients with a precipitating factor (44%) (OR, 2.40 [95% CI, 0.59-10.78]; \(P/H11022\).05 vs cirrhotic controls), and 25 patients without a precipitating factor (93%) (OR, 37.50 [95% CI, 5.44-389.54]; \(P/H11021\).001 vs cirrhotic controls; and OR, 15.63 [95% CI, 2.77-153.72]; \(P/H11021\).001 vs patients with precipitating factors). Survival curves of these groups are presented in the Figure.

Differential characteristics between patients who died and survivors are presented in Table 3. A multivariate analysis of factors potentially associated with mortality showed that the Child-Pugh index, presence of hepatocarcinoma, and serum concentration of urea were associated with mortality, whereas the levels of serum or urine sodium and vasodepressor hormones were not (Table 4). After excluding those patients with kidney failure at the time of admission, only the Child-Pugh index and NE concentrations were independent predictors of mortality (Table 4).

**COMMENT**

Our work has analyzed the incidence, associated findings, and prognosis of dilutional hyponatremia in cirrhotic patients with ascites. One third of patients hospitalized for complications of cirrhosis present with hyponatremia. Our work has analyzed the incidence, associated findings, and prognosis of dilutional hyponatremia in cirrhotic patients with ascites. One third of patients hospitalized for complications of cirrhosis present with hyponatremia.3,6,7 However, the percentage of cirrhotic

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### Table 1. General Characteristics of the Study Population*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 20)</th>
<th>Overall (n = 54)</th>
<th>With Precipitating Factors (n = 27)</th>
<th>Without Precipitating Factors (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 ± 10</td>
<td>64 ± 10</td>
<td>64 ± 8</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Sex, M:F ratio</td>
<td>13:7</td>
<td>33:21</td>
<td>19:8</td>
<td>14:13</td>
</tr>
<tr>
<td>Alcoholic cirrhosis, No. (%)</td>
<td>10 (50)</td>
<td>24 (44)</td>
<td>12 (44)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Previous ascites, No. (%)</td>
<td>12 (60)</td>
<td>48 (89)†</td>
<td>22 (81)</td>
<td>26 (96)†</td>
</tr>
<tr>
<td>Hepatocarcinoma, No. (%)</td>
<td>4 (20)</td>
<td>22 (41)</td>
<td>9 (33)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Peripheral edema, No. (%)</td>
<td>7 (35)</td>
<td>32 (59)</td>
<td>13 (48)</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Pleural effusion, No. (%)</td>
<td>3 (15)</td>
<td>6 (11)</td>
<td>4 (15)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Child-Pugh index</td>
<td>9.9 ± 1.9</td>
<td>8.9 ± 1.9</td>
<td>9.0 ± 1.6</td>
<td>10.8 ± 1.8†</td>
</tr>
<tr>
<td>Serum urea nitrogen, mg/dL§</td>
<td>38 ± 25</td>
<td>83 ± 55[‡]</td>
<td>74 ± 42[§]</td>
<td>92 ± 65[§]</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL¶</td>
<td>0.7 ± 0.3</td>
<td>1.1 ± 0.8[¶]</td>
<td>1.0 ± 0.6[¶]</td>
<td>1.3 ± 0.9[¶]</td>
</tr>
<tr>
<td>Renal failure, No. (%)</td>
<td>4 (20)</td>
<td>31 (57)[¶]</td>
<td>15 (56)[¶]</td>
<td>16 (59)[¶]</td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>135.5 ± 3.5</td>
<td>123.0 ± 5.0[‡]</td>
<td>123.3 ± 5.0[‡]</td>
<td>123.0 ± 5.0[‡]</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.1 ± 0.5</td>
<td>4.8 ± 0.9[¶]</td>
<td>4.9 ± 1.0</td>
<td>4.7 ± 0.9[¶]</td>
</tr>
<tr>
<td>Diuresis, mL/d</td>
<td>1200 ± 447</td>
<td>986 ± 457[¶]</td>
<td>952 ± 550[¶]</td>
<td>679 ± 519¶</td>
</tr>
<tr>
<td>Urinary sodium, mEq/24 h</td>
<td>53 ± 41</td>
<td>4 ± 3[¶]</td>
<td>6 ± 3[¶]</td>
<td>3 ± 2[**]</td>
</tr>
<tr>
<td>Urinary potassium, mEq/24 h</td>
<td>42 ± 17</td>
<td>27 ± 17</td>
<td>27 ± 20</td>
<td>28 ± 17</td>
</tr>
<tr>
<td>Decreased liver size, No. (%)</td>
<td>5 (25)</td>
<td>38 (70)[‡]</td>
<td>15 (56)</td>
<td>23 (85)[‡]</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SD.
†\(P/H11021\).01 vs controls.
‡\(P/H11021\).001 vs patients with a precipitating factor.
§To convert to millimoles per liter, multiply by 0.357.
¶\(P/H11021\).001 vs controls.
**To convert to micromoles per liter, multiply by 88.4.
***\(P/H11021\).01 vs patients with a precipitating factor.

### Table 2. Plasma Renin Activity and Serum Concentrations of Aldosterone and Norepinephrine in the Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n = 20)</th>
<th>Overall (n = 54)</th>
<th>With Precipitating Factors (n = 27)</th>
<th>Without Precipitating Factors (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity, ng/mL per hour*</td>
<td>5.1 ± 5.5</td>
<td>15.2 ± 9.1[‡]</td>
<td>15.0 ± 5.8[‡]</td>
<td>15.4 ± 11.0†</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dL‡</td>
<td>32.4 ± 33.7</td>
<td>91.4 ± 18.2§</td>
<td>94.2 ± 12.2§</td>
<td>89.6 ± 21.5§</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/mL¶</td>
<td>453 ± 357</td>
<td>616 ± 635</td>
<td>414 ± 178</td>
<td>778 ± 813¶</td>
</tr>
<tr>
<td>Plasma antidiuretic hormone, pg/mL¶</td>
<td>4.9 ± 2.7</td>
<td>5.1 ± 2.7</td>
<td>4.5 ± 2.8</td>
<td>5.6 ± 2.6</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112 ± 13</td>
<td>104 ± 13[¶]</td>
<td>108 ± 15</td>
<td>99 ± 98**</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>59 ± 8</td>
<td>57 ± 10</td>
<td>60 ± 11</td>
<td>54 ± 7**</td>
</tr>
</tbody>
</table>

*To convert to nanomoles per liter per hour, multiply by 0.77.
†\(P/H11021\).01 vs controls.
‡To convert to nanomoles per liter, multiply by 0.0277.
§To convert to nanomoles per liter, multiply by 0.00591.
¶\(P/H11021\).05 vs controls.
**To convert to picomoles per liter, multiply by 0.923.
patients admitted to a hospital with hyponatremia is dependent on the admission criteria.

Several characteristics were demonstrated in our patients with hyponatremia. First, hyponatremia occurs predominantly in patients with a reduced liver size. The predictive value of a decreased liver size with reference to the hepatorenal syndrome or to survival has previously been demonstrated.

Second, most of our patients with hyponatremia had previously presented with ascites. Third, blood pressure was significantly decreased, and PRA, concentrations of PAC and NE, and renal resistance index were significantly elevated in our patients with hyponatremia, with values approaching those detected in patients with functional renal insufficiency.

These findings could be the consequence of an arterial vascular underfilling secondary to peripheral arterial vasodilation (spontaneous or after bacterial infection) or to hypovolemia due to hemorrhage. Hyponatremia appeared in the patients with renal insufficiency (31 patients [57%]) or with normal renal function (23 patients [44%]).

Hyponatremia is assumed to be a consequence of an impaired free-water secretion, and nonosmotic secretion of ADH has been considered to play a pathogenic role. Although significantly higher PRA and concentrations of PAC and NE were detected in our patients with hyponatremia, plasma levels of ADH were similar in our hyponatremic patients and nonhyponatremic controls.

Plasma ADH concentrations in patients with cirrhosis have been reported to vary from the reference range to increased concentrations and have not been consistently elevated. This variation has been attributed to measurement methods, to episodic secretion of ADH, and to prolonged ADH half-life. Likewise, ADH concentrations did not correlate with serum sodium levels. The existence of other putative mechanisms implicated in impaired free-water excretion (eg, prostaglandins and atrial natriuretic peptide) might also be considered.

In half of our patients, hyponatremia followed a complication (gastrointestinal tract bleeding or bacterial infection) that could have precipitated activation of the va-
Hyponatremia is an analytical alteration in patients with reduced liver function and activation of hemodynamic mechanisms. Survival is significantly reduced in patients with spontaneous development of hyponatremia.

Hyponatremia is an analytical alteration in patients with reduced liver function and activation of hemodynamic mechanisms. Survival is significantly reduced in patients with spontaneous development of hyponatremia. However, a reduced sodium concentration is not an independent predictor of the risk for death.

CONCLUSIONS

Hyponatremia is an analytical alteration in patients with reduced liver function and activation of hemodynamic mechanisms. Survival is significantly reduced in patients with spontaneous development of hyponatremia.


tive systems. The recovery of normal levels of natremia was detected in every patient who survived those precipitating events.

Spontaneously developed hyponatremia affected our patients with advanced liver cirrhosis. The Child-Pugh index and systolic and diastolic blood pressure of these patients were significantly higher compared with those of patients with hyponatremia induced by precipitating factors. However, analyzed plasma concentrations of vasooactive hormones were similar in patients with spontaneous hyponatremia and those with hyponatremia induced by precipitating factors. No patient with spontaneous development of hyponatremia had a serum sodium concentration within the reference range.

This study has analyzed the possible role of hyponatremia as a prognostic factor in these patients. Although the survival of patients with hyponatremia induced by precipitating factors was similar to that of cirrhotic patients without hyponatremia, the survival of patients with spontaneously developed hyponatremia was significantly lower. The median survival after the diagnosis of spontaneous hyponatremia was 111 days. Most of these patients (23 [85%]) died owing to hepatorenal syndrome.

However, multivariate analysis showed that the Child-Pugh index, presence of hepatocellular carcinoma, and serum levels of urea were associated with mortality. However, multivariate analysis showed that the Child-Pugh index, presence of hepatocellular carcinoma, and serum levels of urea were associated with mortality. In cirrhotic patients without renal insufficiency, a decreased liver size, decreased PRA, and dilutional hyponatremia have been implicated in mortality. However, a reduced sodium concentration is not an independent predictor of the risk for death.

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REFERENCES