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Impact of Hyponatremia On the Severity of Cirrhosis at The Brazzaville University Hospital Center

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1. Abstract

1.1. Introduction: Hyponatremia is the most common water and electrolyte disorder in cirrhosis. Hyponatremia, because of its prognostic value and the difficulties of therapeutic management, has become a hot topic in cirrhotic pathology. The objective of this study was to assess the impact of hyponatremia on the occurrence of complications in cirrhotic patients.

1.2. Patient and Methods: This was a descriptive and analytical study from January 2015 to June 2018, a period of 3 years and 6 months. The serum sodium values were specified on admission. The patients were divided into 2 groups, Group 1 (Na ≥130mmol/l) and Group 2 (Na □ 130mmol/l). We did a univariate analysis and then a multivariate analysis. The predictive factors of hyponatremia and its prognostic impact were evaluated using odds ratios.

1.3. Results: The general population was 144 cirrhotic patients, consisting of 80 men (55.6%) and 64 women (44.6%). The number of patients with hyponatremia was 59, representing a prevalence of 41%. The average age of the patients was 52.8 ± 15.4 years, with extremes ranging from 22-88 years. The non-prescription of b-blockers (25.4%), the severity of cirrhosis (50.8%), malnutrition (88.1%) and dehydration (61%) were the most frequent predictive factors. Hepatic encephalopathy (59.3%), hepatorenal syndrome (49.2%) and hepatocellular carcinoma (64.4%) were incriminated as poor prognostic factors.

1.4. Conclusion: Hyponatremia is the most common hydro-electrolyte disorder in cirrhosis, knowledge of predictive and prognostic factors is necessary for the management of cirrhotic patients. In our study, we observed a predominance of undernutrition and the severity of cirrhosis as predictive factors.

2. Introduction

Cirrhosis is a fibrosing disease that constitutes the terminal stage of chronic liver pathologies. It is a major public health problem. Indeed, the incidence in the world varies from 1.3 to 5.9. In France, the annual incidence is 150 to 200 cases per million inhabitants [1].

Cirrhosis is a frequent condition in the Congo. Studies conducted by J-R Ibara et al reported a hospital prevalence of 22.4% [2].

The usual complications of cirrhosis, namely ascites, gastrointestinal bleeding, infections, hepatic encephalopathy and hepatocellular carcinoma, are responsible for the increase in morbidity and hepatocellular insufficiency.

Hyponatremia is the most common fluid and electrolyte disorder in cirrhosis.

Because of its prognostic value and the difficulties of its therapeutic management, hyponatremia has become a hot topic in cirrhotic pathology. Its prevalence in cirrhosis varies according to the studies. Indeed, a study conducted in 2006 had reported a prevalence of 21.6% and 49.4% respectively for natremia <130mmol/l and natre-

mia ≤135mmol [3].

Hyponatremia places patients at high risk for complications, particularly hepatic encephalopathy (HE), hepatorenal syndrome (HRS), and refractory ascites [4,5]. The occurrence of these complications not only makes the management of patients difficult, but above all increases overall mortality. Epidemiological and clinico-biological studies carried out in Congo had not addressed some of the complications including hyponatremia.

In order to contribute to the improvement of the management of cirrhotic patients, we proposed to evaluate the impact of hyponatremia in the occurrence of complications of cirrhosis by identifying the predictive and prognostic factors of hyponatremia during cirrhosis.

3. Patients and Methods

This is a retrospective and analytical study, ranging from January 4, 2015 to June 30, 2018, i.e. a period of 3 years and 6 months. Epidemiological, clinical and biological data were collected in the Department of Gastroenterology and Internal Medicine at the University Hospital Center of Brazzaville. The target population was patients hospitalized for cirrhosis. The diagnosis of cirrhosis was either confirmed histologically or based on a set of clinical, biological and morphological arguments. All patients aged at least 18 years, having natremia on admission and a complete medical record were included. We excluded patients with hepato renal syndrome (HRS) at the first hospitalization and patients with other causes of hyponatremia apart from cirrhosis (heart failure, kidney failure, gastroenteritis).

Our sample size was 144 patients, divided into 2 groups. Group 1 (G1) consisted of patients with natremia ≥130mmol/l and Group 2 (G2) consisted of patients with natremia ≥ 130mmol/l.

The variables studied were the predictors of hyponatremia namely (age, sex, consciousness disorder, ascites, clinical symptoms of portal hypertension defined by the presence of splenomegaly and collateral venous circulation, liver encephalopathy, undernutrition (assessed by arm circumference (CB) < 26 cm in men and 24 cm in women), dehydration (assessed by intense thirst, hypotonia of eyeballs), diuretics taking, B-blockers taking, prothrombin level, albuminemia and prognostic factors associated with hyponatremia namely (refractory ascite defined according to the criteria of international ascite club, ascite fluid infection, HCC, HE, HRS, digestive hemorrhage, severity of cirrhosis assessed by Child Pugh score, death).

The data entry was done on the excel version 2016 software. Data analysis was done on the SPSS version 20.0 software. Quantitative variables were expressed as mean. The ordinal and nominal qualitative variables were expressed in frequency. Comparative tests were performed with Pearson's chi-square or Fischer's test.

The predictive and prognostic factors of hyponatremia were determined by single logistic regression and then multiple. We included in the multivariate analysis, the parameters having a significance level of 20% in univariate or simple analysis. The significance threshold in univariate and multivariate analysis was set at 5%.

4. Results

4.1. Epidemiology

During the study period, we included 144 cases of cirrhosis. The mean age of the patients was 52.8 ± 15.4 years, with extremes ranging from 22 to 88 years. Men represented 55.6% (n = 80) and women represented 44.4% (n = 64). G1 patients (Na≥130mmol / l) represented 59% (n = 81) and those of G2 (Na≥130mmol / l) represented 41% (n = 59).

4.2. Predictive Factors of hyponatremia

Undernutrition, dehydration, clinical signs of PH, non-use of beta-blockers and severity of cirrhosis were significantly associated with the occurrence of hyponatremia (P 0.05) in univariate analysis. See (Table 1).

After multivariate analysis including parameters with a p <0.2, the parameters remaining in the final model were:

- clinical portal hypertension (p=0,001; OR: 5,072 95% CI: 2,100-12,249),
- undernutrition (p=0,00; OR: 4,876 95% CI: 2,090-11,377),
- Child Pugh class C (p=0,04; OR: 4,16 95% CI : 1,063-16,279)

Table 1: Predictive factors of hyponatremia

Factors	G1 (Na >130) N (%)	G2 (Na<130) N (%)	OR (95% CI)	*p*
Age (years)	53,4 ± 14,8 (20-81)	51,8 ± 16,3 (22-88)	0,993 (0,972-1,015)	0,545
Male sex	54 (63,5)	33 (55,9)	0,729 (0,370-1,435)	0,360
Diuretics taking	47 (55,3)	33 (55,9)	1,026 (0,526-2,003)	0,940
ascite	71 (83,5)	55 (93,2)	2,711 (0,845-8,698)	0,094
Alcohol consumption	19 (22,4)	17 (28,8)	1,406 (0,657-3,007)	0,380
Beta blockers taking	38 (44,7)	15 (25,4)	0,422 (0,204-0,871)	0,020
Hepatic encephalopathy	78 (57,7)	57 (42,2)	2,558 (0,512-12,772)	0,252

Clinical portal hypertension	37 (45,1)	45 (54,8)	4,170 (1,995-8,716)	< 0,001
Dehydration (n=143)	21 (25)	36 (61)	4,696 (2,287-9,642)	< 0,001
Undernutrition	52 (61,2)	52 (88,1)	4,714 (1,914-11,614)	0,001
Low Prothrombin time percentage	66 (77,6)	51 (86,4)	1,835 (0,744-4,529)	0,188
hypo albuminemia	68 (80)	56 (94,9)	4,667 (1,301-16,739)	0,018
Child Pugh				
Class B	52 (61,2)	24 (40,7)	1,846 (0,619-5,507)	0,272
Class C	13 (15,3)	30 (50,8)	9,231 (2,847-29,932)	< 0,001

4.3. Pronostic Factors Associated with Hyponatremia

In our study, gastrointestinal bleeding, disturbed consciousness, refractory ascites, hepatorenal syndrome, hepatocellular carcinoma and death were incriminated as poor prognostic factors related to hyponatremia in univariate analysis. See (Table 2)

After multivariate analysis including parameters with a $p < 0.2$, the parameters that remained in the final model were hepatic encephalopathy ($p = 0.033$; OR: 0.215 95% CI: 0.052-0.884), hepatocellular carcinoma ($p = 0.003$; OR: 3.432 95% CI: 1.505-7.828) and death ($p = 0$; OR: 5.686 95% CI: 2.345-13.788)

The case fatality rate was higher in G2 group compared to G1 group. See (Figure 1). In G2 group, hepatic encephalopathy and hepatocellular carcinoma were significantly associated with death on univariate analysis. See (Table 3).

After multivariate analysis including parameters with a $p < 0.2$; parameters that remained in the final model explaining lethality in this group were the non-taking of β-blockers (p=0.015; OR: 0.078; 95%CI: 0.01-0.604), presence of hepatic encephalopathy (p=0.012; OR: 14.105; 95% CI: 1.796-110.783), and presence of hepatorenal syndrome (p=0.037; OR: 11.657; 95% CI: 1.164-116.709).

However, male sex (p=0.084; OR: 0.162; 95% CI: 0.021-1.280), hypoalbuminemia (p=0.067; OR: 25.506; 95%CI: 0.799-814.704) and presence of hepatocellular carcinoma (p=0.052; OR: 7.079; 95% CI: 0.984-50.920) had low significance.

Table 2: Poor pronostic factors associated with hyponatremia

Factors	**G1 n (%)**	**G2 n (%)**	**OR (95% CI)**	***p***
Consciousness disorder	26 (30,6)	33 (55,9)	2,880 (1,444-5,746)	0,003
Gastrointestinal bleeding	22 (25,9)	30 (50,8)	2,962 (1,465-5,991)	0,003
Hepatic encephalopathy	40 (47,1)	35 (59,3)	1,641 (0,838-3,212)	0,149
Ascitic fluid infection	27 (31,8)	21 (35,6)	1,187 (0,588-2,395)	0,632
Hepatorenal syndrome	18 (21,2)	29 (49,2)	3,598 (1,736-7,458)	0,001
Hepatocellular carcinoma	23 (27,1)	38 (64,4)	4,878 (2,383-9,984)	< 0,001
Refractory ascite	15 (17,6)	26 (44,1)	3,677 (1,722-7,849)	0,001
Death	24 (28,6)	44 (74,6)	7,333 (3,453-15,576)	< 0,001

Table 3: Predictors of death

Factors	Survivors (n=15) n	Deads (n=44) n	OR (95% CI)	*p*
Male sex	11	22	0,364 (0,1-1,318)	0,124
Ascite	13	42	3,231 (0,413-25,255)	0,264
Gastrointestinal bleeding	7	23	1,252 (0,387-4,050)	0,708
Diuretics taking	7	26	1,651 (0,508-5,367)	0,405
Beta blockers taking	8	7	0,166 (0,045-0,605)	0,007
Clinical portal hypertension	14	43	3,071 (0,180-52,395)	0,438
Hepatic encephalopathy	3	32	10,667 (2,556-44,509)	0,001
Undernutrition	14	38c	0,452 (0,05-4,099)	0,481
Hypo albuminemia	13	43	6,615 (0,554-78,942)	0,135
Child Pugh				
Class B	6	18	2 (0,267-14,982)	0,5
Class C	7	23	2,19 (0,303-15,851)	0,437
Ascite fluid infection	5	16	1,143 (0,332-3,937)	0,832
Hepatorenal syndrome	4	25	3,618 (0,996-13,152)	0,051
Hepatocellular carcinoma	6	32	4 (1,172-13,653)	0,027
Refractory ascite	4	22	2,75 (0,759-9,97)	0,124

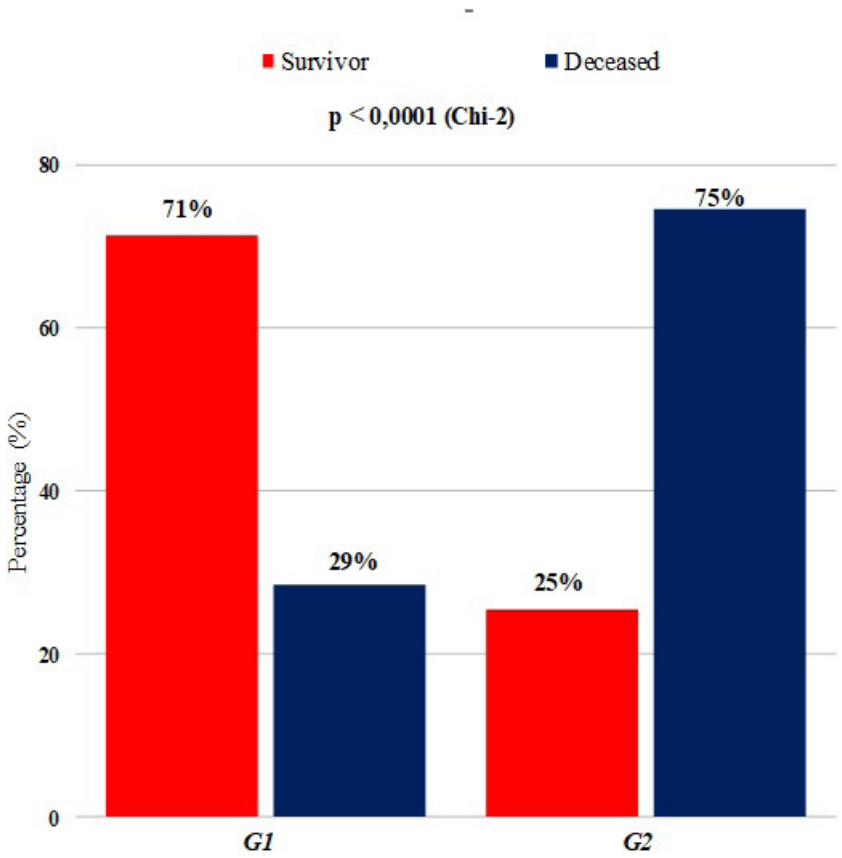

Figure 1: Distribution of lethality in groups

5. Discussion

Our study is limited by the its mono-centric nature which in itself represents a selection bias, because the natremia is a biological parameter whose measurements may vary according to the laboratories. In addition, the difference between the sizes of the two groups reduces the statistical power of our results.

The mean age of our patients was 52.8 ± 15.4 years, this finding can be compared to the study by Ennaifer R et al [6].

In our study the prevalence of hyponatremia in subjects with serum sodium <130 mmol was 41%. Thomas S et al had found a prevalence of 37.9% [7]. This prevalence is close to ours; however, it should be noted that Serste T et al only included patients with cirrhosis with refractory ascites, hence the slight difference in prevalence between the two studies. Ennaifer R et al had found a prevalence of 10.5% [6]. The difference between the study by Ennaifer R et al and ours can be explained by the fact that the patients in their study were classified as stages A and B according to the Child Pugh classification. Ours, however, included patients at all severity stages of cirrhosis.

Our study reports that the severity of cirrhosis was correlated with the occurrence of hyponatremia. This corresponds to the results of other studies [4, 8, 9]. This observation can be explained by the hypersecretion of vasopressin in response to increased splanchnic vasodilation in patients with severe cirrhosis [10,11].

The influence of diuretics in the onset of hyponatremia has been found, but was not statistically significant. Our results are consistent with data from literature [12, 13]. This observation could be explained by the hydro-electrolytic disorders caused by the use of diuretics.

Non-taking of β-blockers was significantly correlated with the occurrence of hyponatremia. This finding could be explained by the contraindication of β-blockers in patients with advanced cirrhosis because of their likely deleterious effects in severe cirrhosis [14,15]. It should be noted that beta blockers have an effect on the mechanism of hyperkinetic syndrome [16], this action leads to a reduction in splanchnic vasodilation which will result in decreased vasopressin secretion. This would explain a low prevalence of hyponatremia in those on beta-blocker therapy.

Age and sex did not influence the occurrence of hyponatremia as described in the literature [4,17,18,19].

Undernutrition and dehydration were significantly associated with hyponatremia although not reported in the literature as predictors. These two parameters can be explained by the lack of nutrient and of water intake in relation to the severity of cirrhosis and by the existence of hypercatabolism during cirrhosis [20].

In our study, hepatic encephalopathy, hepatorenal syndrome and hepatocellular carcinoma were incriminated as poor prognostic factors. Their respective prevalences were 47.1%, 21.2% and 27.1%. Our results are in agreement with other authors's. Indeed, Ennaifer R et al

had found the same prognostic factors [6].

The mortality rate was higher in cirrhotic patients with natremia <130mmol/l. This could be explained by the severity of liver damage. The same observation has been made in numerous studies [21,11,22, 6].

The frequency of death was statistically higher in patients with natremia <130mmol/l. The death predictive factors found in this study, that are liver encephalopathy, use of diuretic and hepatorenal syndrome, may be the explanation.

6. Conclusion

Hyponatremia is the most common fluid and electrolyte disorder in cirrhosis. The severity of the cirrhosis, undernutrition and dehydration are the factors responsible for its occurrence in patients with cirrhosis. It is also, in cirrhotic patients, a poor prognostic factor responsible for morbidity and mortality. The taking of beta-blockers could prevent its occurrence.

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