ORIGINAL

RISK FACTORS OF HEPATIC ENCEPHALOPATHY AFTER AN EPISODE OF UPPER GASTROINTESTINAL BLEEDING IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract

Introduction: Hepatic encephalopathy (HE) is defined as a set of potentially reversible neuropsychiatric alterations secondary to hepatocellular failure and/or portosystemic shunting, being a frequent complication in the evolution of liver cirrhosis. One of the triggers of HE is upper gastrointestinal bleeding (UGB); however, there are few studies that analyse the predisposing factors for the development of HD in this clinical context, as well as its impact on patient prognosis.

Objective: To compare the clinical and blood test characteristics of the group of patients with UGB who develop HE with those who do not, identifying predisposing factors; and to analyse the prognosis of the patients with respect to the group to which they belong.

Methods: Retrospective analysis of a prospective registry including all patients with UGB treated at the Hospital Universitario Virgen de las Nieves between 2013 and 2021, who underwent urgent gastroscopy and presented clinical and/or radiological data of liver cirrhosis. Clinical, biochemical and evolution data (during admission and deferred) were obtained.

Results: Of the 258 patients with liver cirrhosis admitted for UGB, 66 developed HE. Of the variables analysed, only ascites, albumin and urea on admission were found to be independent factors in the development of HE. Furthermore, it was found that the development of HE only significantly increased in-hospital mortality.

Conclusions: The development of HE during an admission for UGB is associated with an increased risk of in-hospital

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mortality, with liver function variables and urea on admission being the only parameters independently related to the development of HE, with no significant patient-intrinsic data or variables regarding the type of bleeding.

Keywords: liver cirrhosis, hepatic encephalopathy, upper gastrointestinal bleeding.

Introduction

Hepatic encephalopathy (HE) is a group of potentially reversible neuropsychiatric alterations secondary to hepatocellular insufficiency and/or portosystemic shunting, being a frequent complication in the evolution of liver cirrhosis. Given the wide variety of symptoms with which HE expresses itself, the clinical practice guideline made by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) defines it as ``A cerebral dysfunction caused by hepatic insufficiency and/or portosystemic shunt; manifesting as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma''[1]. The abrupt or progressive loss of hepatocyte functions, as well as, collateral portosystemic hepatic circulation produces an imbalance between hepatic elimination of toxic substances from the intestine, which pass directly into the general circulation, causing neuronal dysfunction, cerebral edema, intracranial hypertension and finally hepatic encephalopathy[2]. The mechanisms underlying HE are multifactorial. Initially, the appearance of encephalopathy in cirrhotic patients was considered to be a direct effect of the increase in serum ammonium levels, generated by the intestinal flora from dietary proteins that through the portal circulation passes to the liver where it is metabolized by the urea cycle. The decrease in hepatic clearance of ammonium induces hyperammonemia, being directly toxic to the central nervous system, acting especially indirectly on glutamatergic and GABAergic neurotransmission[3]. However, ammonia is currently considered a necessary but not sufficient risk factor for the development of HD in the progression of liver cirrhosis. Recent studies have identified other factors such as inflammatory cytokines, manganese, benzodiazepine-like compounds, mercaptans, aromatic amino acids and the microbiota as being involved in the pathophysiology of encephalopathy[4,5].

Specifically in liver cirrhosis, the development of HE results in a decompensated stage of the disease that occurs in response to one or more triggers. The most common triggers are infections including spontaneous bacterial peritonitis, urinary tract infections, respiratory infections, skin infections, among others. Other factors that also favor the development of HE are electrolyte disorders, diuretic overdose, constipation and digestive bleeding[1,2]. However, not only triggering factors are necessary but also the existence of predisposing factors such as the existence of minimal hepatic encephalopathy, a history of an episode of hepatic encephalopathy, sarcopenia, hyponatremia, renal failure, high bilirubin levels, hypoalbuminemia, use of PPIs, or treatment with beta-blockers[2,5].

There are few studies that analyze the incidence and predisposing factors for the development of HD after an episode of gastrointestinal bleeding in cirrhotic patients. Studies such as that of Sharma P *et al.*[6] and Wen J *et al.*[7]; analyze this aspect in a secondary manner when attempting to demonstrate the efficacy of lactulose as primary prophylaxis of hepatic encephalopathy after bleeding from esophageal varices. A more recent study identifies Child Pugh stage C, hypokalemia less than 3.5 mmole/L, leukocytosis greater than 10000 U/mm3 and hemoglobin less than 8 gm/dL as predisposing factors for the development of HD after upper gastrointestinal bleeding due to esophageal varices (HDAV)[8].

The aim of our study is to analyze the development of HE in patients with liver cirrhosis admitted to our hospital for melenas and/or hematemesis, with the objective of identifying predisposing factors to favor early diagnosis, as well as to study the repercussion of HE in the evolution of these patients.

Material and methods

Study design and population

This is a prospective registry in which we consecutively included all those patients seen in the Emergency Department of the University Hospital Virgen de las Nieves with a diagnosis of upper gastrointestinal bleeding (UGB) between 2013 and 2021. From this registry, we performed a subanalysis of patients with liver cirrhosis admitted for this reason and compared those who developed HE during admission and those who did not.

The inclusion criteria were:[1] age over 18 years;[2], UGB defined as the presence of hematemesis and/or melena; and[3] presenting diagnostic, clinical and radiological criteria for liver cirrhosis at the time of admission. Exclusion criteria were[1] Refusal to sign the informed consent for the study or refusal to undergo endoscopy on admission; and[2] Clinical instability or inadequate baseline situation contraindicating urgent endoscopy.

Patients were followed up during hospitalization and 6 months after hospital discharge. All patients included in the study underwent urgent gastroscopy, defined as gastroscopy

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performed within 12 hours of admission to the emergency department.

The criteria for defining the development of hepatic encephalopathy during admission were those included in the 2022 EASL guidelines, classifying severity according to the West Haven criteria[1].

Variables studied

Demographic variables, comorbidities, pharmacological treatments prior to admission or the episode of UGB, including the use of proton pump inhibitors (PPIs), hemodynamic status and laboratory tests at the time of arrival at the emergency department were collected. The occurrence of hepatic complications including the development of ascites, hepatic encephalopathy and spontaneous bacterial peritonitis were documented. Data were collected on the etiology of UGB, endoscopic treatment performed, as well as the need for additional treatments.

In relation to the prognostic variables studied, in-hospital mortality was defined as that occurring during hospitalization; and deferred mortality as that occurring in the first 6 months after the episode of UGB and hospital stay.

Statistical analysis

Statistical analysis was performed using Python v3.10.1 and R v4.3.2. Categorical variables were compared using the Chi-square test or Fisher's exact test, depending on the minimum expected cell size (>5). Continuous variables were evaluated using the Shapiro-Wilk test for normality, the Levene test for homogeneity of variances and, subsequently, the t-test for independent samples was applied, with or without Welch's correction, or the Mann-Whitney test. Finally, multivariate analysis was performed to identify independent risk factors for variables with statistically significant differences, calculating Odds Ratios (OR) and their 95% confidence intervals (95%CI).

Results

Of the total of 258 cirrhotic patients admitted with UGH, 152 (59%) had variceal upper gastrointestinal bleeding and 106 (41%) had non-variceal upper gastrointestinal bleeding. A total of 66 (19%) patients developed hepatic encephalopathy.

Patients who developed hepatic encephalopathy had a higher frequency of active enolism (57.69% vs. 38.72% p=0.02) and a higher score on the MELD scale (18 vs. 13 p= 0.0002). Regarding analytical alterations at admission, HE patients differed in creatinine (1.37 vs1.6 p=0.003), bilirubin (4, 78 vs 2.18 p=0, 000015), albumin (2.63 vs 3.04 p= 0.000056), INR (1.77 vs 1.65 p= 0.005), ascites (48% vs 29.1% p= 0.015) and urea (95.72 vs 70.53 p=0.00017). Table 1 shows the remaining patient characteristics.

Regarding prognostic variables, HE patients presented a higher mortality rate during admission, without finding statistically significant differences for the rest of the variables studied.

There were 31 deaths in HE patients, 21 of which occurred during admission.

After multivariate analysis by logistic regression, albumin (OR 0.41 CI95% 0.23-0.7), the presence of ascites (OR 1.65 CI95% 1.01-2.71) and urea on admission (OR 1.01 CI95% 1-1.02) were identified as independent risk factors for HE, as shown in table 2. The inclusion of both urea and creatinine in the logistic regression allowed the multivariate model to be corrected for the latter, ruling out the existence of a confounding effect. Additionally, a partial correlation between HE and urea was performed, using creatinine as a control variable. It was observed that the positive correlation between the two variables was maintained (Rho = 0.141 p= <0.01). All this evidences that urea acts as a predictor of hepatic encephalopathy independent of renal function, as determined by creatinine.

Discussion

There are few studies that analyze the factors that favor the development of HE in the context of gastrointestinal bleeding. As indicated in the introduction, most of them analyze this aspect in a secondary manner.

The most widespread conception in the literature is that HE is a decompensated stage of liver cirrhosis, so that those patients with worse liver function as assessed by the Child Pugh Score or the MELD score are at greater risk of developing it. Our study shows that patients who develop an episode of HE have worse liver function, as measured by a higher MELD score. In addition, analytical parameters associated with liver dysfunction such as hyperbilirubinemia, hypoalbuminemia, coagulation disorders or the presence of ascites correlate significantly with respect to the development of HE in the univariate analysis; only albumin on admission and the presence of ascites were significant factors related to liver function in the multivariate analysis. These data are similar to those reported in the literature, where it is described that advanced liver cirrhosis defined as Child Pugh C would be the

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most relevant clinical parameter in the development of hepatic encephalopathy after variceal bleeding[7,8].

Certainly, in the literature, not only has the role of liver failure been analyzed, but also analytical parameters such as alterations in the blood series or the existence of ionic alterations have been proposed as predisposing factors for HE. In our study, no significant differences were observed in hemoglobin levels at admission in both groups. This differs from the pre-existing literature in which we found two studies where hemoglobin lower than 8 mg/dl is identified as a significant predictor in the development of hepatic encephalopathy[7,8]. Another analytical alteration proposed as a triggering factor for HE is hypokalemia[8]. However, in our analysis, no significant differences were observed in both groups with respect to potassium levels.

Our study does find urea on admission to be a predictor of the development of HE after an episode of UGB. It could be suggested that the elevation of urea on admission could be altered secondary to a worsening of renal function due to a situation of low output in relation to digestive losses or due to a situation of decompensation of liver cirrhosis[9]. However, as indicated in the results section, the existence of a confounding effect of creatinine was ruled out, and the relationship between urea and HE persisted.

Regarding variables related to patient comorbidities, as in the literature, no significant differences were found. We even analyzed possible confounding factors such as the presence of a history of HE episodes and the presence of TIPs. These variables had little impact on our "results" given that only one patient had required TIPS placement for refractory variceal UGB and only 13 (19.6%) of the patients had had previous

Hepatic encephalopathy	Present (N=66)	Absent (N=192)	P-value
Age	59 ± 13	62 ±12	0.46
Male sex	60%	16 %	0.37
MELD	18.08 ±7	13 ±7,67	0.00002
Alcohol	57.69%	38.72%	0.02
Tabacco	37.25%	33.66%	0.75
PPIs	50%	48%	0.84
Hemoglobin	8.2 ±2.23	8.9 ± 2.44	0.31
Bilirubin	4.78 ±7.7	2.18 ± 3.24	0.000015
Albumin	2.63 ± 0.57	3.04 ±1.28	0.000056
INR	1.77 ± 0.62	1.65 ±0.82	0.0056
Creatinine	1.37 ± 0.7	1.6 ± 6.41	0.0036
Platelets	125945 ±72209	140502 ±94082	0.66
Ascites	48.07%	29.12%	0.015
Urea	95.72 ±57.69	70.53 ±42.63	0.00017
Active endoscopic bleeding	38,46%	32,04%	0,47
Rebleeding	19,23%	15,6%	0,67
Need for intervention (endoscopy, transfusion, surgery or radiology)	59,61%	65,04%	0,79
Days of admission	11,75 ± 12	10,43 ±12,22	0,32
Mortality admission	33%	16%	0,00016
Mortality delayed	16%	12%	0,19

Table 1. ***Baseline characteristics of patients developing hepatic encephalopathy.***

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Variables	OR (95% CI)	P-value
Bilirubin	1,07 (1 - 1,16)	0,064
Albumin	0,41 (0,23 - 0,7)	0,0017
INR	1,10 (0,73 - 1,56)	0,58
Creatinine	0,77 (0,5 - 1,12)	0,18
Ascites	1,65 (1,01-2,71)	0,04
Urea on admission	1,01 (1 – 1,02)	0,0005

***Table 2.* Multivariate logistic regression results. Independent factors of hepatic encephalopathy, with ascites, hypoalbuminemia and elevated urea on admission being the most relevant predictors in the model.**

episodes of hepatic encephalopathy, requiring secondary prophylaxis with rifaximin and maintenance lactulose.

In our cohort, the development of hepatic encephalopathy during admission for UGB did not lengthen hospital stay; however, it did significantly increase mortality during admission. With respect to deferred mortality, relevant differences were observed in the descriptive analysis, with a higher percentage of deaths in the group that developed HE, although this difference was not statistically significant.

The results obtained in our study suggest the possible predictive role in the development of HE of analytical and clinical characteristics present on admission after UGB. Among the alterations analyzed, urea is postulated as one of the most relevant variables with respect to HE, acquiring a new prism as a predictor of hepatic complications, beyond its diagnostic role in gastrointestinal bleeding. Nevertheless, parameters related to liver function continue to be a fundamental pillar in the early diagnosis of the development of HE.

The main limitation of our investigation is the inclusion of patients from a single center, which may imply a lower applicability of the results. However, since it is a reference center, patients of different complexities have been included, which may mitigate this limitation. On the other hand, this study, unlike others previously performed, includes episodes of gastrointestinal bleeding, both variceal and of other origin, which provides more information on the pathophysiology of HE in this clinical context, beyond variceal UGB. On the other hand, we must consider the sample size as a limitation, given that we have only been able to analyze 66 patients who have developed HE, which is a small cohort of patients. However, an advantage of the study is that it is a prospective registry of patients, with data collection carried out systematically by the research team.

For the time being, more studies with larger sample sizes are needed to clarify how these variables influence the development of HE, and predictive scores can be developed in the future to help us make an early diagnosis.

Conclusions

After the results obtained, we can say that HE developed during admission for UGB in cirrhotic patients implies a higher risk of mortality during admission, and it may be useful to assess albumin, the presence of ascites and urea on admission, since they correlate with a higher risk of HE and may be factors that allow us to make an early diagnosis in the future.

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