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CLINICAL STUDIES

Risk factors for hepatic encephalopathy in patients with cirrhosis and refractory ascites: relevance of serum sodium concentration

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Abstract

Hyponatraemia is common in patients with advanced cirrhosis and is associated with remarkable changes in brain cells, particularly a reduction in myoinositol and other intracellular organic osmolytes related to the hypo-osmolality of the extracellular fluid. It has been recently suggested that hyponatraemia may be an important factor associated with the development of overt hepatic encephalopathy (HE). To test this hypothesis, we retrospectively analysed the incidence and predictive factors of overt HE using a database of 70 patients with cirrhosis included in a prospective study comparing transjugular intrahepatic portosystemic shunts (TIPS) vs large-volume paracentesis in the management of refractory of ascites. Variables used in the analysis included age, sex, previous history of HE, treatment assignment (TIPS vs large volume paracentesis plus albumin), treatment with diuretics, serum bilirubin, serum creatinine and serum sodium concentration. Laboratory parameters were measured at entry, at 1 month and every 3 months during follow-up and at the time of development of HE in patients who developed this complication. During a mean follow-up of 10 months, 50 patients (71%) developed 117 episodes of HE. In the whole population of patients, the occurrence of HE was independently associated with serum hyponatraemia, serum bilirubin and serum creatinine. In conclusion, in patients with refractory ascites, the occurrence of HE is related to the impairment of liver and renal function and presence of hyponatraemia.

Patients with advanced cirrhosis frequently develop hepatic encephalopathy (HE), a disorder of neurological function that encompasses a wide spectrum of clinical signs and symptoms ranging from minimal changes in neuropsychological function to profound coma (1, 2). In marked contrast with the large amount of existing information on risk factors for other complications of cirrhosis, such as spontaneous bacterial peritonitis, variceal bleeding or hepatorenal syndrome (3–7), there is little information on factors predictive of the development of HE. Earlier studies in patients treated with surgical portosystemic shunts as well as recent studies in patients treated with transjugular intrahepatic portosystemic shunts (TIPS) indicate that the degree of portosystemic shunting represents a major risk factor for the development of HE in patients with cirrhosis (8–11). Unfortunately, however, there is no reliable method for the quantification of portosystemic shunting in patients with cirrhosis in clinical practice. On the other hand, although the occurrence of HE is probably related to the severity of liver failure, there have been few studies assessing the predictive capacity of liver function tests in assessing the risk of occurrence of HE in patients with cirrhosis (12, 13). Finally, there are other conditions not

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directly related to porto-systemic shunting or liver failure that are frequently present in patients with cirrhosis and may theoretically represent a risk factor for the development of HE. A particularly interesting condition is hyponatraemia, which is associated with marked changes in the central nervous system because of the reduction in plasma osmolality (14–17). Recent studies have suggested that serum sodium concentration is a risk factor for the development of HE (18, 19). Moreover, there is no specific information in patients with refractory ascites, Therefore, in the current study, we evaluated the predictive factors of HE in a series of patients with cirrhosis and refractory ascites.

Patients and methods

Study design

This study represents a retrospective analysis of patients with cirrhosis and refractory ascites included in a prospective study aimed at comparing large-volume paracentesis and albumin vs TIPS in patients with cirrhosis and refractory ascites (20). The study was performed in nine centres in two countries (United States of America and Spain) and involved 70 patients with cirrhosis and refractory ascites. The protocol of the study was approved by the investigational review board of each of the nine centres involved. All patients provided written informed consent before study entry. Patients were considered to have refractory ascites when there was no response to low sodium diet and spironolactone 400 mg/day and furosemide 160 mg/day or they developed diuretic-induced complications, according to the definition of the International Ascites Club (21). The exclusion criteria have been reported previously (20).

Before randomization, clinical and biochemical parameters of the patients were recorded and then patients were randomized to therapy either with large-volume paracentesis plus intravenous albumin (8 g/L of ascites removed) or TIPS insertion (Wallstent; Schneider, Minneapolis, MN, USA). The TIPS treatment strategy was to reduce the portal pressure gradient below 12 mmHg, because ascites rarely develops with a gradient below this level (22). After treatment, patients were discharged from hospital. Physical examination and renal and liver function tests were performed at baseline and at least one, 3, 6 and 12 months after inclusion. After treatment with paracentesis plus albumin or TIPS, some patients were administered variable doses of diuretics to prevent the recurrence of ascites and/or oedema when clinically indicated. If urine sodium did not increase above 20 mEq/day despite diuretic therapy, diuretics were withdrawn. Patients were then followed for a median follow-up of 5.4 months (range 0.3–46 months), and the occurrence of HE was recorded prospectively and included in the database.

Hepatic encephalopathy was defined as any episode of grade I or greater, according to the West Haven criteria (23) and treated with standard therapy including oral lactulose or lactitol with or without bowel cleansing.

Hyponatraemia was defined as serum sodium concentration < 130 (mEq/L).

Statistical analysis

The main objective of this study was to assess factors predictive of HE. Because HE is a recurrent event and some parameters that can be associated with HE may change over time, we used the conditional model proposed by Cai and Prentice (24). This is an extension of the Cox model that considers different baseline hazard functions for observations with a different number of episodes of the event during the study period, and stratifies the analysis by this factor. A robust estimation for the standard error of risk evaluations was made assuming independence between subjects but not within subjects. Time-dependent covariates, both related and unrelated to liver function, were assessed in the multivariate model. Serum bilirubin was selected among parameters related to liver function. Among parameters unrelated to liver function, serum sodium and serum creatinine were selected for the analysis. Values of serum bilirubin, serum sodium and serum creatinine included in the analysis were those obtained at the time of inclusion and follow-up visits performed at month 1 and later every 3 months, as well as values obtained at the time of diagnosis of HE in patients developing this event during follow-up.

Because treatment with diuretics has been described as a possible precipitating factor of HE (25), the administration of diuretics was also examined as a time-dependent variable and included in the analysis as a categorical variable (treatment with diuretics vs no diuretic therapy). Other variables used in the analysis of factors predictive of HE included demographic variables, such as age and sex, treatment assignment for refractory ascites (TIPS or large-volume paracentesis) and a previous history of overt HE.

A univariate analysis was first performed and variables with a P value < 0.10 were evaluated in the multivariate Prentice, Williams and Peterson proportional hazard model. Estimations of risks were made using 95% confidence intervals and their associated P-value. Continuous variables are expressed as mean $\pm$ standard deviation (SD); categorical variables are expressed as frequency and percentages. For categorization of the variables, we used the median value as a cut-off. All reported P values are two-sided; a P value of < 0.05 was considered to be statistically significant. The analysis was performed using R for Windows aver 2.6.1 [The Foundation for Statistical Computing and SPSS 14 for Windows (SPSS Inc., Chicago, IL, USA)].

Results

Characteristics of the patients

Clinical and demographical characteristics and liver and renal function tests of the whole group of patients are

Table 1. Baseline characteristics of patients at the time of inclusion in the study

Variables	Patients ($n = 70$)
Age (years)	58 ± 11 (37–74)
Sex (M/F)	50/20
Aetiology of cirrhosis	
Hepatitis C virus infection	24
Alcohol	34
Other*	12
Child–Pugh	
Class (A/B/C)	0/42/28
Score	9 ± 1.5 (7–12)
MELD score	14 ± 4 (6–16)
Ascites	70
Previous hepatic encephalopathy	27
Previous gastrointestinal bleeding	20
Bilirubin (mg/dl)	2.2 ± 1.5 (0.4–7.9)
Albumin (g/L)	29 ± 6 (18–46)
Prothrombin time (%)	67 ± 18 (30–100)
Serum creatinine (mg/dl)	1.4 ± 0.5 (0.7–2.55)
Serum sodium (mEq/L)	129 ± 6 (117–141)

MELD score was calculated using the following web address http://www.mayoclinic.org/gi-rst/mayomodel5.html. A direct measurement of INR was not available. INR was calculated according the following formula: (prothombin time of patient/control prothrombin time)^{ISI}, ISI being the international sensitivity index for thomboplastin.

Values are mean ± SD or number of patients. Values in brackets are ranges.

*Alcoholic plus viral hepatitis in seven patients, cryptogenic cirrhosis in four patients and hepatitis B virus in one patient.

MELD, model for end-stage liver disease.

shown in Table 1. Twenty-seven patients had 39 episodes of overt HE before enrolment in this study. Precipitating factors of HE were as follows: diuretic administration in 17 patients, bacterial infection in three and gastrointestinal bleeding in two. No precipitating factors could be identified in the remaining 17 episodes. Eleven patients were being treated with non-absorbable disaccharides at the inclusion in this study.

Occurrence of hyponatraemia during follow-up

Thirty-four of the 70 patients (49%) developed at least one episode of hyponatraemia during follow-up. Thirty-one episodes occurred in patients with paracentesis and 31 episodes occurred in the group of TIPS.

Occurrence of hepatic encephalopathy

Fifty (71%) of the 70 patients included in the study developed a total of 117 episodes of HE (60 grade I/II and 57 grade III or IV). The mean number of episodes of HE per patient was 1.7 ± 0.2 (range 0–11). Twenty-one of the 50 patients who developed HE during follow-up had had a previous history of encephalopathy, while the remaining 29 patients developed '*de novo*' HE. In the entire series, the probability of developing HE was 55 % at 3 months and 70 % at 1 year.

Predictive factors of hepatic encephalopathy

The Prentice Williams and Peterson univariate model for multiple events revealed the following variables as predictors of HE ($P < 0.10$): serum sodium concentration, serum bilirubin, serum creatinine, age and therapeutic intervention for ascites (TIPS vs large-volume paracentesis plus albumin) (Table 2). The variables that were associated with an independent prognostic value for HE in the Prentice Williams and Peterson multivariate model are shown in Table 3. Hyponatraemia, serum bilirubin and serum creatinine were independently associated with the development of HE. These three variables were included as categorical in the multivariate analysis because the relationship between a continuous variable and the event may follow a non-proportional relationship. Treatment with TIPS was significantly associated with the development of overt HE in the univariate analysis, and showed a trend to be significantly associated with overt HE in the multivariate analysis.

Discussion

The current study reports an investigation of factors related to the development of HE in a population of patients with cirrhosis and refractory ascites included in a randomized comparative study between large-volume paracentesis plus albumin and TIPS. The main objective of the current study was to assess factors predictive of HE in a group of patients with advanced cirrhosis, being at a high risk of development of HE. Hyponatraemia is a common complication of patients with refractory ascites, which is associated with poor prognosis. Therefore, patients with refractory ascites constitute a unique population to study the relationship between hyponatraemia and HE because of the high frequency of these two complications. As half of the patients included in this study received treatment with TIPS, which is well known to predispose HE, this factor was included in the analysis.

A time dependent analysis was used, which implies that for variables that may change over time, the analysis takes into account not only the value of these variables obtained at entry into this study but also values obtained at regular intervals during follow-up. Therefore, this method allows for a better assessment of a possible relationship between a specific event (HE in the current study) and variables that may change during follow-up compared with the classical time-independent analysis, which only includes the value of each of the variables obtained at baseline.

The univariate analysis revealed five variables as predictive factors of HE. Three variables were time-dependent variables, including serum bilirubin, serum creatinine and serum sodium concentration, while the other two variables were a time-independent variable, age (age was analysed as a time-independent variable because the median follow-up was of less than 1 year) and therapeutic intervention (TIPS vs paracentesis plus albumin). In the multivariate analysis, serum bilirubin,

Table 2. Univariate analysis of predictive factors of overt hepatic encephalopathy

	Hazard ratio	95% confidence interval	*P*
Hyponatraemia (< 130 mEq/L)	1.45	1.15 – 1.84	0.002
Serum sodium (mEq/L)	0.937	0.9 – 0.975	0.001
Serum bilirubin ≥ 1.9 mg/dl	1.86	1.33 – 2.6	< 0.001
Serum bilirubin (mg/dl)	1.1	1.03 – 1.17	0.006
Serum creatinine ≥ 1.3 mg/dl	1.32	1.04 – 1.66	0.021
Serum creatinine (mg/dl)	2.01	1.45 – 2.81	< 0.001
Age (years)	1.02	1 – 1.04	0.030
TIPS	1.25	0.998 – 1.56	0.051
Previous hepatic encephalopathy	1.19	0.787 – 1.81	0.407
Sex (male)	0.995	0.78 – 1.25	0.965
Diuretic treatment (yes)	0.991	0.758 – 1.29	0.945

(Prentice, Williams and Peterson models).
Laboratory variables were analysed both as continuous variables and categorical variables, using the median value to categorize the variables.
TIPS, transjugular intrahepatic portosystemic shunt.

Table 3. Variables included in the multivariate analysis

	Hazard ratio	95% confidence interval	*P*
Hyponatraemia	**1.35**	**1.04–1.75**	**0.027**
Serum creatinine ≥ 1.3 mg/dl	**1.48**	**1.11–1.96**	**0.007**
Serum bilirubin ≥ 1.9 mg/dl	**1.87**	**1.35–2.59**	**< 0.001**
TIPS	1.23	0.98–1.53	0.072
Age (years)	1.01	0.98–1.03	0.530

In bold are those variables with an independent predictive value in the development of overt HE in the multivariate analysis (Prentice, Williams and Peterson models) in all patients included in the study.
TIPS, transjugular intrahepatic portosystemic shunt.

serum creatinine and serum sodium were independently associated with the development of HE. Treatment with TIPS showed a trend to be significant. This lack of significance was probably related to the relatively low sample size.

In the multivariate analysis, serum bilirubin was independently associated with HE. This finding is not unexpected as serum bilirubin is an excellent marker of liver function and HE is related to the severity of liver failure (26–28). Serum creatinine was also independently associated with HE in the whole group of patients. It has been described previously that serum creatinine is independently associated with cognitive dysfunction in patients with cirrhosis (29). In addition, in patients with cirrhosis, the kidneys are considered to be important for ammonia metabolism. In rats with acute and chronic liver failure, the kidneys switch from ammonia production to ammonia removal (30). Moreover, a direct relationship between ammonia and serum creatinine has been observed in patients with cirrhosis (29). Therefore, the presence of renal failure may impair the capacity of the kidneys to remove ammonia from the circulation. The results of this study, together with previous data, suggest that the impairment of renal function is an important risk factor of HE in cirrhosis.

The relationship between serum sodium and overt HE has been recently suggested in two studies (18, 19). The study published by Riggio *et al*. (18) showed that low serum sodium was an independent factor related with the development of overt HE in patients treated with TIPS with covered stent grafts. The second study, performed by our group, evaluated the effect of serum sodium on the development of overt HE in a group of patients with cirrhosis and ascites not treated with TIPS (19). These studies suggest the existence of a pathogenic relationship between hyponatraemia and HE in different groups of patients with cirrhosis.

The relationship between low serum sodium levels and increased risk of HE may be explained, at least in part, by the important changes that occur in the brain in the setting of low serum sodium concentration (14–16, 31). Briefly, when serum sodium falls, and so does the osmolality of the extracellular fluid, water moves into the brain cells in order to attain the osmotic equilibrium between the extracellular and intracellular spaces, leading to cell swelling. Subsequently, there is a cellular release of solutes, including electrolytes and organic osmolytes, as homeostatic response to prevent cell swelling and cerebral oedema. Low cerebral levels of organic osmolytes, particularly myoinositol, have been reported in patients with cirrhosis and hyponatraemia (15, 31). These cerebral changes induced by low serum sodium concentration have to be discussed in light of the current pathogenic model of HE, which considers that in cirrhosis, ammonia and other neurotoxins induce a low-grade cerebral oedema because of astrocyte swelling secondary

to increased intracellular levels of glutamine (32, 33). This low-grade cerebral oedema brings about multiple alterations in astrocyte function, including changes in gene expression and oxidative/nitrosative stress, which affect glioneuronal communication and disturb neurological function, leading to HE. In this context, a progressive reduction in serum sodium concentration may contribute to an exhaustion of the cell systems to counteract cell swelling and increase the risk of HE. Further studies are required to assess the relationship between serum sodium concentration and HE in patients with cirrhosis as well as the pathogenic mechanisms responsible for such an association.

The main limitation of this study is that it was not specifically designed to assess predictive factors of HE, but rather to compare the effects of two different treatment modalities (large-volume paracentesis plus albumin and TIPS) in patients with refractory ascites. Nevertheless, it should be pointed out that HE was one of the secondary end-points of this study and all episodes of HE were prospectively recorded in the case report forms and included in the database. Likewise, analytical variables used in the current time-dependent analysis were also recorded prospectively at regular intervals during follow-up. Therefore, both the primary event assessed in the current study and the variables analysed as predictive factors were recorded prospectively.

In conclusion, the current study using a time-dependent statistical analysis in patients with cirrhosis and refractory ascites identified serum sodium concentration, serum bilirubin and serum creatinine as predictive factors of HE. This indicates that not only factors directly related to liver failure but also other conditions that may affect cerebral function, such as hyponatraemia and renal impairment, are important determinants of HE in cirrhosis.

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