SARCOPENIA REPRESENTS A RISK FACTOR FOR THE DEVELOPMENT OF HEPATIC ENCEPHALOPATHY AFTER TRANSJUGULAR INTRAHEPATIC PORTOSYSTHEMIC SHUNT

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Abbreviations: SMI: skeletal muscle index; HE: hepatic encephalopalthy; TIPS: transjugular intrahepatic portosysthemic shunt; sHR: subdistribution hazard ratio.

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ABSTRACT

Introduction/Aim: Hepatic Encephalopathy (HE) is a major problem in patients treated with TIPS. The aim of our study was to investigate whether a decrease in muscle mass may independently influence the occurrence of HE after TIPS.

Patients/Methods: 46 consecutive cirrhotic patients submitted to TIPS were included. All patients had a computed tomography scan at the level of the third lumbar vertebrae to determine the skeletal muscle index (SMI); sarcopenia was defined by sex-specific cut-offs. The incidence of the first episode of HE after TIPS, taking into account the competing risk nature of the data (death or liver transplantation), was estimated. **Results.** Twenty-six patients (57%) were affected by sarcopenia. Twenty-one (46%) patients developed overt HE during 7±9 months after TIPS. All of them were sarcopenic according to SMI. The difference in the incidence of post TIPS HE between the patients with or without sarcopenia was highly significant ($p < 0.0001$). At multivariate analysis, MELD score: (sHR: 1.16, CI:1.01-1.34, p=0.043) and sarcopenia: (sHR:31.3, CI:4.5-218.07, $p<0.001$) were independently associated to post TIPS HE. **Conclusions.** Muscle wasting, probably by reduce the handling of ammonia, is a risk factor for the development of HE after TIPS. Sarcopenia should be considered in the selection of the patients submitted to TIPS. In sarcopenic patients, the amelioration of nutritional status before TIPS may be a possible goal to decrease the incidence of HE.

INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is currently used for the treatment of complications of portal hypertension, mainly variceal rebleeding and refractory ascites[1]; the most frequent complication after this procedure is hepatic encephalopathy (HE), that has been reported in 30-55%[2] of patients. Unfortunately, no pharmacological treatment has been until now proved to be able to reduce the incidence of post-TIPS HE[3], thus, the patients' selection remains the only method to try to reduce the incidence of this complication.

Alterations in nutritional status are frequently associated with liver disease; in advanced cirrhosis malnutrition has been reported in 65–90% of patients and it is associated with mortality[4]. Sarcopenia, a condition of loss of muscle mass, is associated with cirrhosis' complications, including HE[5]; the rationale for this relationship derives from the possible involvement of muscle in ammonia metabolism and trafficking.

The patients submitted to TIPS are frequent malnourished, but no data exist on the impact of nutritional status on post-TIPS HE. Therefore, the aim of the study was to investigate the relationship between sarcopenia and the incidence of HE in cirrhotic patients submitted to TIPS.

METHODS

From January 2013 to December 2014, 46 consecutive cirrhotic patients submitted to TIPS were included in this prospective study. Liver function, clinical and biochemical data were evaluated in each patient at admission. During the month before hospitalization, all patients had a computed tomography scan and for the determination of muscle mass, the axial plane passing through the intersomatic disk between L3-L4 was chosen. Images were analyzed with SliceOmatic V4.3 software (Tomovision, Montreal, Quebec, Canada), by two observers (SN, BL) with 5 years of experience in radiology. Muscle cross-sectional area was normalized for stature^2 to obtain the skeletal muscle index (SMI) in cm^2/m^2. The cut-offs for the identification of sarcopenic patients (L3 SMI $\leq$38.5 cm^2/m^2 for women and $\leq$52.4 cm^2/m^2 for men) were previously utilized in cirrhotic

patients[6]. All TIPS procedures were carried out by the same radiology team, using PTFE-covered, dilated to 10 mm.

The incidence of the first episode of HE taking into account the competing risk nature of the data (death or liver transplantation) was estimated. A grade II HE or higher was considered an episode of overt HE[7] and the patients were censored as HE+ patients.

The data are reported as mean ± SD. We use the Gray method for cumulative incidence estimation and (penalized) Fine and Gray models for sub-distribution hazard ratios. The final multivariate model was chosen by minimizing Akaike Information Criterion.

RESULTS

The 46 patients included in the study (34M/12F) had a median age of 58.6±9.1 years, a MELD score of 11.3±3.3 and a Child-Pugh score of 7.6±1.5; TIPS indication was equally distributed between variceal bleeding and refractory ascites. Sarcopenia according to SMI cut-off was present in 26 patients (57%).

Compared to the patients without sarcopenia, patients with muscle depletion were older (61.2±8.8 vs 55.1±8.5 yrs;p=0.01), affected by a more severe liver disease according to MELD score (12.2±3.1 vs 10.2±3.1;p=0.01) and more often had a previous episode of HE (5vs0;p=0.03) before TIPS.

After TIPS, all patients had amelioration of ascites and/or bleeding cessation; no serious adverse events were recorded. During a mean follow up of 7 ± 9 months, 21 patients (46%) developed overt HE and all of them were sarcopenic, 12 patients died and 6 were transplanted. All patients with HE were hospitalized in our department and treated with lactulose per os and enemas; all precipitated events were investigated and treated; no patient developed refractory HE. The difference of post TIPS HE was highly significant ($p < 0.0001$) between the patients with or without sarcopenia. Univariate competing risk regression for time to HE after TIPS placement is reported in Table 1. At multivariate analysis MELD score: (sHR 1.16, CI 1.01-1.34, p=0.043) and Sarcopenia:

(sHR 31.3, CI 4.5-218.07, $p<0.001$) were independently associated with post TIPS HE development.

DISCUSSION

This study indicates, for the first time, that muscle wasting in cirrhotic patients constitutes a strong and independent risk factor for the occurrence of HE after TIPS placement.

In cirrhotic patients, the relationship between protein malnutrition, survival and occurrence of complications is known[5]. In this study, sarcopenia was diagnosed by CT scan, which is now considered the optimal tool to quantify the skeletal muscle mass and for the identification of sarcopenic cirrhotic patients [6].

As far as the patients submitted to TIPS, until now, some studies evaluated the nutritional status and body composition in cirrhotic patients before and after the procedure[8], but none related the presence of protein malnutrition to the occurrence of HE. The mechanism underlining to the relationship between muscle wasting and HE may be related to the reduction of the capacity of ammonia removal[5].

In conclusion, our study indicates that muscle wasting favours the development of hepatic encephalopathy in cirrhotic patients after TIPS placement. Consequently, the amelioration of nutritional status before TIPS may be a possible goal to decrease the incidence of HE.

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