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Hepatic encephalopathy in patients with non-cirrhotic portal hypertension: Description, prevalence and risk factors

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ABSTRACT

Background: Hepatic encephalopathy (HE) is a common complication of cirrhosis but it is less studied in patients with non-cirrhotic portal hypertension (NCPH).
Aims: To describe the prevalence of cognitive impairment (overt and covert HE) in NCPH patients and to identify the risk factors for its development.
Methods: 51 patients with NCPH, 35 with chronic portal vein thrombosis (PVT) and 16 with idiopathic non-cirrhotic portal hypertension (INCPH), were evaluated for the presence of previous or present overt HE (OHE). The psychometric hepatic encephalopathy score and the SCAN battery were used to detect the presence of covert HE (CHE). 34 compensated cirrhotic patients were used as control. In NCPH patients, abdominal scans were performed to detect the presence of shunts.
Results: None of the patients experienced OHE at evaluation while 5.7% of PVT and 12.5% of INCPH patients referred at least one documented episode of previous OHE, similarly to patients with cirrhosis (14.7%). Even if lower than in patients with cirrhosis (64.7%), a considerable proportion of patients with chronic PVT (34.3%) and INCPH (25%) had CHE ($p = 0.008$). The presence of a large portal-systemic shunt was the only factor significantly correlated to cognitive impairment in NCPH patients.
Conclusion: HE is a tangible complication of NCPH and is mainly related to the presence of portal-systemic shunts.

1. Introduction

Hepatic encephalopathy, at least in the western world, is mainly associated to liver cirrhosis (type C-HE; C from cirrhosis) and is considered a consequence of both the liver damage and the presence of portal-systemic shunts. HE has also been described in animals and in patients with congenital portal-systemic shunts [1,2] (Type B-HE; B from bypass), suggesting that the presence of a large portal-systemic shunt, by reducing the detoxification of gut derived toxins, may induce alterations in the central nervous system even in the absence of significant liver damage. In the western world, portal-hypertension not due to cirrhosis is an uncommon condition, mainly caused by chronic portal vein thrombosis (PVT). More recently, a disorder characterized by portal hypertension not associated to liver cirrhosis or chronic PVT [3–5] has been better defined [6,7] and named as idiopathic non-cirrhotic portal hypertension (INCPH). Patients with non-cirrhotic portal hypertension (NCPH), as well as cirrhotic patients, may develop collaterals and, in some cases, large spontaneous portal-systemic shunts, which may predispose the patients to HE. In liver cirrhosis the relationship between large portal-systemic shunts and HE is supported by a number of clinical observations such as the high incidence of HE after surgical [8] or radiological [9] porto-caval anastomosis, the relationship between the diameter of the shunt and the severity and recurrence of HE episodes and the amelioration of the neurological symptoms after the reduction of the shunt calibre in patients submitted to transjugular intrahepatic portosystemic shunt (TIPS). Moreover, in cirrhotic patients the presence of large portal-systemic shunts have been related to a severe and persistent

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form of HE, poorly responsive to medical treatment [10], which can be ameliorated by the closure of the shunt [11,12,13].

The aims of the present study were to describe the prevalence of the different grades of cognitive impairment (overt HE and minimal/covert HE) in 51 adult Italian patients with NCPH (35 with chronic PVT and 16 with INCPH) and to identify the risk factors for its development, focusing on the role of large portal-systemic shunts.

2. Patients and methods

Among 90 patients affected by NCPH seen and followed up in our Centre for the Study of Portal Hypertension, fifty-one patients available for HE assessment during the study period (from October 2014 to June 2015) were included in the study. Thirty-five were affected by chronic portal vein thrombosis (PVT) and 16 by idiopathic non-cirrhotic portal hypertension (INCPH), according to the diagnostic criteria suggested in the EASL Clinical Practice Guidelines on Vascular diseases of the liver [14].

Portal hypertension was diagnosed on the presence of oesophageal varices or other portal-systemic collaterals and attributed to chronic PVT when imaging techniques (Doppler ultrasound and contrast-enhanced CT-scan) showed the presence of portal cavernoma, defined as the development of a network of tortuous collateral vessels bypassing the obstructive area at hepatic hilum. Neoplastic portal vein obstruction was excluded on the basis of imaging studies and negative tests for serum tumour markers. Cirrhosis was excluded on the absence of causes of chronic liver diseases, normal results of liver function tests and on the absence of advanced fibrosis on liver elastometry. In 8 patients liver cirrhosis and/or obliterative portal venopathy was excluded on the basis of histological features.

In patients with signs of portal hypertension the diagnosis of idiopathic non-cirrhotic portal hypertension (INCPH) was based in all cases on the absence of liver cirrhosis at liver biopsy and on the exclusion of portal and sovrahepatic veins obstruction at Doppler Ultrasound and CT-scan. Other causes of liver disease (chronic viral hepatitis, alcoholic liver disease, non alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis and Wilson disease) were also excluded by a complete diagnostic clinical and laboratory workout.

Thirty-four cirrhotic patients belonging to the class A of Child-Pugh, submitted to the same neuropsychological evaluation, were enrolled as control group. The diagnosis of liver cirrhosis was based on clinical, laboratory and histological features.

Both cirrhotic and NCPH patients were receiving drugs reducing portal hypertension (i.e., β-blockers) when appropriate (large oesophageal varices); none of the patients was taking statins. No patients were receiving lactulose or rifaximin at the moment of evaluation.

2.1. HE assessment

The hepatic encephalopathy assessment included the evaluation of overt HE, previous overt HE and minimal/covert HE.

At enrolment the presence and grade of overt HE, according to West Haven Criteria [15], was evaluated in all patients by a pool of standardized questions as suggested by Amodio et al. [16] and previously described [17,18].

Previous overt HE has been defined as the presence in the patient's history of at least one episode of overt HE (grade II or more), documented in a clinical record of a previous hospitalization.

The presence of minimal/covert HE was assessed by two different batteries of tests [19]: the psychometric hepatic encephalopathy score (PHES) and the Scan battery which explore different domains of cognitive impairment but also have different levels of difficulty: being the scan test more complex than the PHES [20]. PHES includes the digit-symbol-test (DST), the trail-making-test A (TMT-A) and B (TMT-B), the serial-dotting-test (SDT) and the line-tracing-test (LTT). Each test was scored against age and education-adjusted norms for the Italian population. PHES is the sum of integer scores of each test computed from the adjusted Z values, as follows: score -3 for $Z \leq -3$, score -2 for $-3 < Z \leq -2$, score -1 for $-2 < Z \leq -1$, score 0 for $-1 < Z < 1$, score 1 for $Z \geq 1$. A PHES ≤ -4 was considered abnormal [21]. The Scan battery is a series of 3 computerized tests of increasing complexity, including the simple visual reaction time (SVRT), the choice visual reaction time (CVRT) and the scan test reaction time (STRT) [20]. A total Z score of the whole Scan battery (tZSB) can be calculated and it results from the value of STRT for the patients that are able to perform all the three tests of the battery, from the Z score of CVRT minus 7.5 for those who are unable to perform the sole STRT (the most difficult test of the battery), and from the Z score of the SVRT for the patients who are unable to perform either CVRT and STRT [20]. A total Z SCAN battery ≤ -2 was considered abnormal.

The tests were administered in a quiet and well-lit room by a hepatologist with expertise on hepatic encephalopathy during a single session of about 45 min; interruption for rest was allowed as soon as fatigue or reduced compliance was suspected. Exclusion criteria were: neuropsychiatric disorders such as dementia (patients with Mini-Mental State Examination <26 were excluded), use of psychotropic drugs, active alcohol intake, language and visual barriers and lack of consent or compliance for the psychometric assessment. Accordingly, 10 patients were excluded from the psychometric evaluation: 2 for language barrier and 8 (all among cirrhotic patients) for active alcohol intake.

The purpose of the study was clearly explained to all the patients before obtaining their written informed consent. The "Sapienza" University of Rome Ethical Committee approved the collection of data of the patients for prognostic studies (Rif.1720/01.10.09).

2.2. Portal-systemic shunts evaluation

In 41 of 51 patients with NCPH (28 with chronic PVT and 13 with INCPH), the presence of spontaneous portal-systemic shunts has been evaluated on the basis of contrast-enhanced CT/MRI abdominal scans. The evaluation of CT/MRI scans was carried out by a skilled (8 year experience) body radiologist (PL), who was blind to the results of the neuropsychiatric assessment. In the presence of shunts, their location and type were evaluated and recorded. Spontaneous portal-systemic shunts have been classified as follows:

- direct splenorenal shunt (Fig. 2, panel A) (tortuous varicosities between the splenic vein and the left renal vein in the absence of varicosities along the gastric wall),
- splenogastrorenal or indirect splenorenal shunt (Fig. 2, panel B_1–B_2–B_3) (an anastomosis between a short gastric vein, supplying gastric and perigastric varices, and the left renal vein via the left inferior phrenic vein with connection with the splenic vein). In addition to the identification of spontaneous portal-systemic shunts, the presence of iatrogenic shunts (surgical and/or transjugular intrahepatic portosystemic shunt-TIPS) was also evaluated,
- gastrorenal shunt (Fig. 2, panel C_1–C_2) (tortuous vessels around the stomach that shunts blood towards an enlarged left renal vein without connection with the splenic vein).

2.3. Statistical analysis

Data are expressed as mean ± SD, unless specified otherwise. Comparison between 2 groups was performed by chi square test or