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Central Nervous System Alterations in Liver Cirrhosis: The Role of Portal-Systemic Shunt and Portal Hypoperfusion

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The role of portal-systemic shunting and portal liver hypoperfusion in the pathophysiology of central nervous system dysfunction of cirrhosis is not yet well defined. It is well known that one of the most important collateral vessels (CV) is a patent paraumbilical vein (PUV) but there is controversy regarding its clinical significance. We have evaluated the relationships between neuropsychological and EEG alterations, ammonia plasma level (NH_4), hepatic function, and portal hemodynamics (Doppler Ultrasound) in 95 cirrhotic patients. Patency, diameter, or flow of PUV or the presence of other CV were not related to an increased prevalence of neuropsychological or EEG abnormalities. Patients with effective portal flow (EPF = portal flow – PUV flow) lower than 692 mL/min (median) had a significantly higher risk of failing the neuropsychological test, or of having an altered EEG. Low EPF and prothrombin time (<50%), and high NH_4 ($\geq$51 μmol/L) were independent predictors of an abnormal EEG. Considering both low EPF and the numerosity of CV, only low EPF was found to explain EEG alterations. In conclusion, portal liver hypoperfusion and decreased liver function were associated with an increased risk of central nervous system dysfunction in cirrhotic patients, whereas PUV patency *per se* was not.

Key words: Subclinical hepatic encephalopathy; liver cirrhosis; psychometric tests; cognitive alterations; portal-systemic shunt; Duplex Doppler Ultrasound.

INTRODUCTION

Central nervous system dysfunction (CNSD) is frequently present in cirrhotic patients, ranging from subclinical alterations to severe coma. In the 1950s, Sherlock et al. (1954) and White et al. (1955) emphasized the pathophysiological role of ammonia coming from the bowel and reaching the systemic circulation (and thus the brain) bypassing the liver through the portal collateral vessels. Consequently, this syndrome is referred to as "portal-systemic encephalopathy."

The role of portal-systemic shunting of neurotoxic material has emerged from the entire pathophysiologic hypothesis on hepatic encephalopathy (Sherlock and Dooley, 1993), although this cannot be said for that regarding zinc deficiency (Reding, Duchateau, and

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Bataille, 1984). The importance of portal-systemic shunting was confirmed by the high prevalence of overt hepatic encephalopathy in cirrhotic patients with portal-cava shunt (Fischer and Faloon, 1957; Read et al., 1968; Richardson and Moffat, 1953) and, more recently, also with transjugular intrahepatic portosystematic stent shunt (TIPS) (Jalan et al., 1995; Martin et al., 1993; Ochs et al., 1995; Sanyal et al., 1994). Moreover, hepatic encephalopathy was found to be associated with the presence of large spontaneous portal collateral vessels (Lam, Juttner, and Reynolds, 1981; Ohnishi et al., 1985; Summerskill et al., 1956). At any rate, even though shunting of portal blood is a key factor for the occurrence of hepatic encephalopathy, the degree of hepatic failure and of liver perfusion must also be taken into account (Kardel, Ramsoe, and Norby, 1975). Indeed, surgical and radiological portal systemic shunts are always characterized by a marked decrease in hepatic portal perfusion and function (Riggio et al., 1996; Spina et al., 1993). On the contrary the papers by Kugler et al. (1992) assessing liver function by galactose elimination capacity, aminopyrine breath test, the elimination of indocyanine green clearance, and liver perfusion by hepatic sorbitol clearance suggested that cognitive dysfunction in minimum or mild encephalopathy is related to reduced metabolic capacity rather than to reduced liver blood flow or increased portal-systemic shunting.

The aim of this study was to assess whether CNSD is related to portal hemodynamic features assessed by Duplex Doppler Ultrasound (DDU).

PATIENTS AND METHODS

Patients with clinically or histologically proven liver cirrhosis who had undergone neurophysiological and neuropsychological assessment and a hemodynamic evaluation of the portal district by DDU during the same week in our Unit between 1997 and 2000 were considered eligible for the study.

The diagnosis of cirrhosis was based on case history, clinical examination, biochemical, endoscopic, and ultrasound findings, or on liver biopsy. The diagnostic criteria were presence of hepatic stigmata on routine clinical examination together with biochemical indexes of decompensated liver disease (low serum albumin, high bilirubin, prolonged prothrombin time, low platelets count), endoscopic or ultrasonic signs of portal hypertension, or a history of previous decompensation (ascites, jaundice, bleeding from oesophageal varices). The diagnosis was confirmed by liver biopsy when needed (40 patients). The exclusion criteria were technically inadequate ultrasound examination due to poor echogenic window because of excess gas in the bowel, presence of overt hepatic encephalopathy, heart failure of any origin (NYHA class >1; i.e., “no limitations, ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations”), chronic obstructive lung disease or other severe lung disease with respiratory failure ($PaO_2 < 60$ mm_{Hg} and/or $PaCO_2 > 50$ mm_{Hg}), renal failure (defined as serum creatinine value >250 μmol/L and/or blood urea nitrogen >25 mmol/L); psychiatric or neurological illness; history of vascular cerebral disease; and history of consumption of psychotropic drugs and/or alcohol abuse in the 6 months preceding the study (documented by an accurate interview confirmed by a relative).

In all the enrolled cirrhotic patients, hepatic function, the presence of CNSD, and portal haemodynamics were evaluated.

• ***Hepatic Function Assessment***

Albumin plasma level, serum bilirubin, prothrombin time (PT), and ammonia plasma level (NH_4) were considered as hepatic function parameters and were measured by routine techniques.

• ***Central Nervous System Alterations***

The presence of CNSD was evaluated by neuropsychological and neurophysiological tools.

• ***Neuropsychological Assessment***

Each patient underwent the Number Connection Test (NCT) (Conn et al., 1977) and the Symbol Digit Test (SDT) (Wechsler, 1955). The NCT was made of 25 circles containing numbers from 1 to 25 randomly printed on a sheet of paper. The task of the subject was to connect the circles in sequential order as rapidly as possible. An initial demonstration was performed to familiarize the subjects with the test. The SDT consists of five rows, each containing 25 cases for a total of 125 cases; each one contained one out of nine symbols in the top half of the square and was empty in the bottom half. On the top of the form there was the key to the test: nine cases containing the nine symbols on the upper half and the corresponding digits on the bottom half. The task of the subject was to fill as many as possible of the empty half-squares with the digit corresponding to each symbol in 90 s. The operator filled in the first three cases, the subsequent seven served as a practice. Time was measured from the tenth case onward.

Number Connection Text was expressed as *Z* score (standard deviation from the expected values calculated by a predictive model, with age and education as predictors) and was considered altered if $Z > 2.3$ (Amodio et al., 1999a). The results of the SDT were considered altered if they were below the 10th percentile of the normal population, according to Lezak (1995).

• ***Neurophysiological Assessment***

In all cirrhotic patients, spontaneous closed-eye-EEG activity was recorded by digital EEG equipment (Brainquick 3200 Micromed, Mogliano Veneto, Italy). Attention was paid to avoid somnolence and artifacts. A standard 21-channel cup (Micromed, Italia) was used, and the electrodes were placed according to the "10–20" international System (Klem et al., 1999). The ground was FpZ, the reference Oz. Impedance was kept lower than 5 kΩ. Each channel had its own analogic-to-digital converter; signals were digitally filtered in the range 0.33–120 Hz. Sampling frequency was 256 Hz and conversion resolution was 0.19 V/digit. After visual inspection to exclude artifacts, the EEG tracing was assessed by spectral analysis (S-EEG). The spectral analysis was carried out on the tracing of the derivations T3-O1 and T4-O2 in the frequency range 1–25.5 Hz. The analysis was carried out on the tracing on 50 epochs of 2 s each for a total of 100 s. The parameters considered in the analysis were the mean dominant frequency (MDF) and the relative power of the delta, theta, alpha, and beta rhythms. The rhythms were defined as follows: delta (1–3.5 Hz), theta (3.5–8 Hz), alpha (8–13 Hz). Grade I of hepatic encephalopathy was considered when theta relative power was >35% and Grade II when MDF was <7.3 (Amodio et al., 1999b).

• ***Duplex Doppler Ultrasound Assessment***

All subjects were studied in the morning after an overnight fast, with a Toshiba Sonolayer SSA-270 with Color Doppler and 3.5 MHz convex electronic probe by two skilled operators. Interobserver variability was as good as previously reported (Bolognesi et al., 1997).

The portal vein was visualized longitudinally in B-mode and the sample volume was positioned inside it immediately after the cross-point between the hepatic artery with the portal trunk with a $<60^\circ$ angle between the vessel and the ultrasound beam. Portal blood flow mean velocity (PBV) was calculated according to Sabba et al. (1995) as mean maximum velocity multiplied by 0.57 and expressed as centimeter per second. Portal blood flow (PBF) volume was calculated as PBV multiplied by cross-sectional area, calculated from the portal vein diameter (PVD), and thus assumed to be circular, and was expressed as milliliter per minute. The presence of a paraumbilical vein (PUV) arising from the left branch of the portal vein was verified by Echo–Doppler. The sample volume was positioned inside it halfway along its course through the left lobe of the liver with a $<60^\circ$ angle between the vessels and the ultrasound beam. Paraumbilical vein blood flow mean velocity (PUV-Vel), PUV diameter, and paraumbilical blood flow volume (PUV-F) were measured and calculated as carried out in the portal vein (Sabba et al., 1995). Moreover, PBF volume actually perfusing the liver (effective portal flow) was calculated as PBF minus PUV-F (Sacerdoti et al., 1995). The presence of other major collateral vessels was recorded (coronary vein, gastrosplenorenal vein) as described by Subramanyam et al. (1983) and Dokmeci et al. (1981).

STATISTICS

Results were expressed as mean $\pm$ SD, or as median values and interquartile intervals when they did not fit a Gaussian distribution (Shapiro–Wilk test).

The assessment of risk factors was performed by simple or stepwise multivariate logistic regression analysis. Continuous variables were divided into quartiles and considered as factors. The biochemical indexes of liver disease of different groups were analyzed by the Student's *t* test; correlations between variables were verified by the Pearson's *r* test. Frequencies were compared by the Fisher exact test.

For the analysis, the packages "Statistica 5.1" (StatSoft, Inc., Tulsa, USA) and "Egret 1.1" (Cytel Software Corporation, Cambridge, USA) were used.

RESULTS

Of the 121 cirrhotic patients considered for the study, 95 satisfied the inclusion criteria. The age was 53 $\pm$ 10 years (mean $\pm$ SD). Seventy-one were males. Forty-four percent of the patients had alcoholic or mixed etiology cirrhosis, 50% had virus-related cirrhosis and 6% other kinds of liver cirrhosis (primary biliary cirrhosis, hemocromathosis, cryptogenetic cirrhosis). Twenty-nine percent were class A, 53% class B and 18% class C according to the Child-Pugh classification [percent values for PT were used in the classification according to Merkel et al. (1991)]. The main biochemical features of the patients are shown in Table 1.

Table 1. The Main Biochemical Features of the Patients

Variable	Reference range	Mean value	Alterations (%)
Albumin (g/L)	41–47	31.8 ± 6.9	88
Serum bilirubin (μmol/L)	1.7–17	42.3 ± 52.8	77
Prothrombin time (%)	75–112	59.7 ± 13.3	67
NH_4 (μmol/L)	10–35	54.9 ± 25	68

Psychometric and Electrophysiological Findings

On average, the NCT was performed in 57.1 ± 32.3 s ($Z = 1.12 \pm 1.81$); within 90 s 27 ± 13 blanks of the SDT were filled in. The NCT was altered in 19% cirrhotic patients, the SDT in 40% cirrhotic patients; 41% cirrhotic patients had altered either the NCT or the SDT.

The S-EEG was abnormal in 46% cirrhotic patients: 33% patients had Grade 1 alterations, 13% patients had Grade 2 alterations according to a modified Van der Rijt's classification as in use in our laboratory (Amodio et al., 1999b).

DDU Findings

No collateral vessel was detected in 41% patients, a patent PUV was found in 33% patients, a patent PUV associated with other collateral vessels was found in 26% patients. The hemodynamic parameters of cirrhotic patients are shown in Table 2. Patients with a patent PUV had PVD and PBF significantly higher than patients without one (14.3 ± 3.1 vs. 13.0 ± 2.0 mm, $p = 0.02$; 994 ± 466 vs. 792 ± 413 mL/min, $p = 0.03$, respectively). Moreover, patients with low EPF had a higher prevalence of at least one patent collateral vessel than did patients with high EPF (70% vs. 30%, $\chi^2 = 4.8$, $p = 0.03$).

Table 2. The Hemodynamic Characteristics of the Patients

	Mean ± SD	Median	Lower–upper quartile
Portal vein diameter (mm)	13.7 ± 2.7	13.7	12.3–15
Portal blood flow (mL/min)	893 ± 450	827	554–1186
Effective portal flow (mL/min)	711 ± 501	692	425–1001
Paraumbilical vein diameter (mm)	6.7 ± 3.3	6	4–9
Paraumbilical vein blood flow (mL/min)	363 ± 482	165	57–402

Note: Portal blood flow is calculated as portal blood flow mean velocity (mean maximum velocity multiplied by 0.57 and expressed as centimeter per second) multiplied by cross-sectional area, calculated from the portal vein diameter, and expressed as milliliter per minute. Paraumbilical vein blood flow is calculated as paraumbilical blood flow mean velocity (mean maximum velocity multiplied by 0.57 and expressed as centimeter per second) multiplied by cross-sectional area, calculated from the paraumbilical vein diameter, and expressed as milliliter per minute. Effective Portal Flow = portal blood flow – paraumbilical vein blood flow.

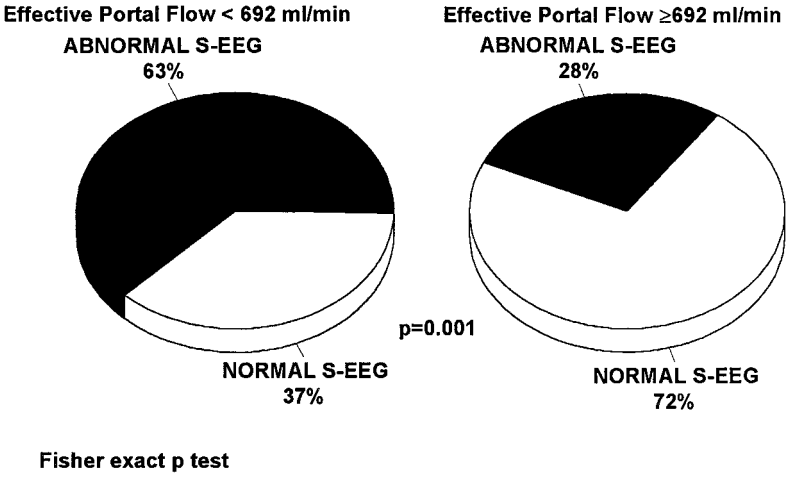

Figure 1. Prevalence of abnormal EEG spectral analysis in cirrhotic patients with effective portal flow lower or higher than the median value (692 mL/min). Frequencies were compared by Fisher exact *p* test.

Relationship between DDU Variables and Psychometric or EEG Findings

Among DDU variables, only EPF was associated with the presence of CNSD: in patients with an EPF lower than 692 mL/min (median value), the risk of failing NCT or SDT (Fig. 1) as well as the risk of an altered S-EEG (Fig. 2) were increased. In addition, considering both

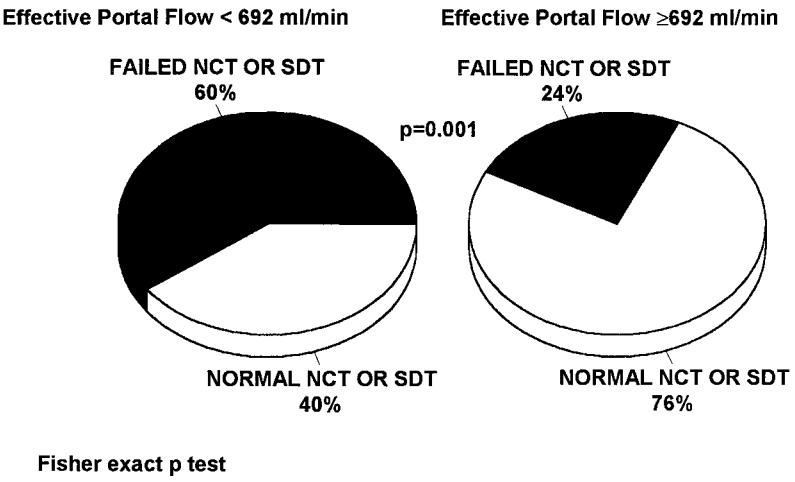

Figure 2. Prevalence of failed Number Connection Test or Symbol Digit Test in cirrhotic patients with effective portal flow lower or higher than the median value (692 mL/min). Frequencies were compared by Fisher exact *p* test.

Table 3. Risk of Failing Number Connection Test or Symbol Digit Test and of Having an Altered S-EEG in Patients with Different Hemodynamic Conditions

	S-EEG altered		NCT or SDT altered	
	OR ($CI_{95\%}$)	*p*	OR ($CI_{95\%}$)	*p*
Effective portal flow <692 mL/min (median)	5.3 (1.8–10.4)	<0.01	4.7 (1.9–11.7)	<0.01
Paraumbilical vein patency	1.4 (0.6–3.2)	0.45	0.7 (0.31–1.7)	0.49
Paraumbilical vein diameter				
1st quartile	0.5 (0.1–2.0)	0.32	0.9 (0.2–3.2)	0.86
2nd quartile	2.5 (0.6–9.9)	0.18	0.4 (0.1–1.9)	0.23
3rd quartile	2.0 (0.5–7.4)	0.28	0.6 (0.2–2.3)	0.49
4th quartile	1.4 (0.4–5.7)	0.60	1.2 (0.3–4.9)	0.75
Paraumbilical vein flow				
1st quartile	0.7 (0.2–2.8)	0.63	1.2 (0.3–4.5)	0.73
2nd quartile	2.5 (0.6–9.9)	0.18	0.1 (0.02–1.2)	0.07
3rd quartile	1.0 (0.3–3.4)	0.96	0.5 (0.1–2.0)	0.30
4th quartile	2.1 (0.5–8.9)	0.28	1.9 (0.5–7.6)	0.37

Note: Paraumbilical vein blood flow is calculated as paraumbilical blood flow mean velocity (mean maximum velocity multiplied by 0.57 and expressed as centimeter per second) multiplied by cross-sectional area, calculated from the paraumbilical vein diameter, and expressed as milliliter per minute. Effective portal flow – portal blood flow – paraumbilical vein blood flow.

EPF and the number of collateral vessels, only EPF was found to explain MDF variability (two ways ANOVA: $F = 8.9$, $p = 0.004$). Patency, diameter, or flow of PUV were not related to an increased prevalence of psychometric nor EEG abnormalities (Table 3).

Relationships between the Indexes of Liver Function and Psychometric or EEG Findings

Among the indexes of liver function, only a low serum albumin (<28 g/L) was associated with NCT or SDT alterations (OR = 2.9, $CI_{95\%} = 1.0–8.3$, $p < 0.05$), whereas PT <50% (lower quartile) and serum bilirubin >50 μmol/L (upper quartile) were found to be associated with S-EEG alterations (OR = 6.9, $CI_{95\%} = 1.8–26.4$, $p < 0.01$, and OR = 3.5, $CI_{95\%} = 1.0–12.1$, $p < 0.05$, respectively). NH_4 levels were found to be linked to S-EEG alterations (OR = 3.3, $CI_{95\%} = 1.2–8.8$, $p < 0.02$), whereas they were not linked to NCT or SDT alterations (OR = 1.3, $CI_{95\%} = 0.5–3.5$, $p = 0.53$) or with PUV patency (OR = 1.1, $CI_{95\%} = 0.5–2.9$, $p = 0.73$).

Relationship between DDU Variables and Indexes of Liver Function

Patients with a patent PUV had a lower PT (63 $\pm$ 14 vs. 57 $\pm$ 11 mg/dL, $p = 0.04$). Serum bilirubin was correlated with the diameter of the PUV ($r = 0.21$, $p = 0.04$) and with EPF ($r = –0.21$, $p = 0.04$). The Child-Pugh score was correlated with EPF ($r = –0.24$, $p = 0.02$). At any rate the correlations were weak and cirrhotic patients with an EPF in the lower quartile did not differ significantly from the others as far as the biochemical indexes of liver function were concerned.

Table 4. Predictors of an Altered EEG Assessed by a Multiple Stepwise Logistic Regression

	COEFF.	SE	*p*	OR
Effective portal flow <692 mL/min (median)	1.34	0.55	0.014	3.8 ($CI_{95\%}$ = 1.3–11.1)
Prothrombin time <50% (lower quartile)	1.34	0.67	0.046	3.8 ($CI_{95\%}$ = 1.0–14.2)
Ammonia plasma level 51 μmol/L (median)	1.104	0.55	0.046	3.0 ($CI_{95\%}$ = 1.0–8.9)

Note: Effective portal flow = portal blood flow − paraumbilical vein blood flow.

Risk of Psychometric or EEG Abnormalities Assessed by Multivariate Analysis

The relative weight of the hemodynamic variables (PVD, PVF, EPF, PUV diameter, and PUV-F) and of the biochemical indices of liver failure (serum albumin, serum bilirubin, PT, and NH_4) in predicting psychometric or S-EEG alterations was assessed by stepwise logistic multiple regression: EPF, PT, and NH_4 were found to be independent predictors of an abnormal S-EEG (Table 4, Fig. 3) whereas only EPF (but not the biochemical indices of liver failure) was found to be a significant predictor of NCT or SDT alterations (OR = 3.0, $CI_{95\%}$ = 1.5–5.9, $p < 0.01$).

DISCUSSION

The results of this study suggest that CNSD is linked to the reduction of EPF and impaired liver function rather than to the patency of a PUV or of other collateral vessels.

Portal-systemic shunting plays an important role in the development of hepatic encephalopathy in cirrhotic patients with surgical or spontaneous portal-cava shunt (Fischer and Faloon, 1957; Ohnishi et al., 1985; Read, McCarthy, Ajdukiewicz, and Brown, 1968;

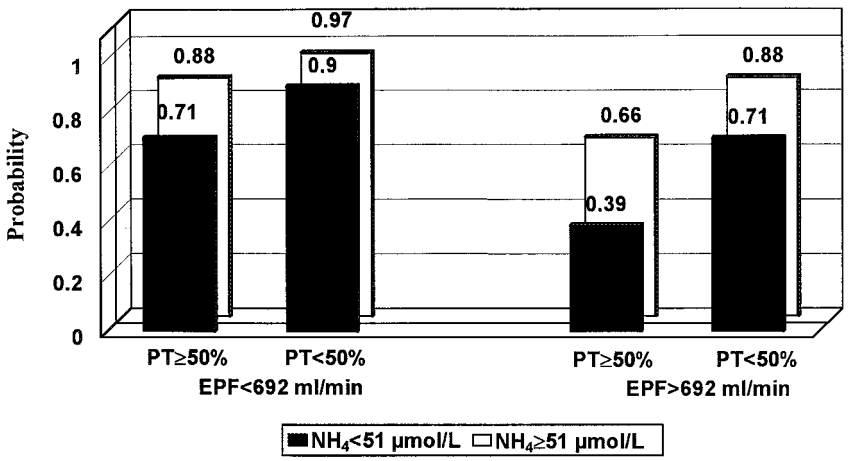

Figure 3. Probability of having an abnormal EEG spectral analysis in cirrhotic patients based on effective portal flow, prothrombin time, and ammonia plasma level.

Richardson and Moffat, 1953; Summerskill, Dawson, Sherlock, and Steirer, 1956). A higher risk of developing encephalopathy in cirrhotic patients with large spontaneous shunts or with patent PUV than in cirrhotic patients without overt portal-systemic shunts was found by Lam et al. (1981). In addition, Rikkers et al. (1978) found a high prevalence of psychometric and EEG alterations in otherwise normal cirrhotic patients with surgical portal-systemic shunt. Recently, Gupta et al. (2000) found a greater prevalence of PUV patency in patients with overt hepatic encephalopathy (9/13; 69%) as compared with those without hepatic encephalopathy. Nonetheless, the common clinically considered association between PUV patency and encephalopathy was not evident in our patients. At any rate, it should be noted that, even if there is a clear relationship between surgical portal-cava shunt or TIPS and minimal hepatic encephalopathy, about two thirds of shunted patients do not develop overt or minimal hepatic encephalopathy after surgery or TIPS (Riggio et al., 1989). Therefore, the presence of portal-systemic shunts is not sufficient *per se* to cause hepatic encephalopathy, but it is only a risk factor.

In contrast, in our study, a significant association was found between abnormal psychometric or neurophysiologic findings and portal hepatic perfusion: patients with EPF below the median value had a risk of showing signs of CNSD about five times higher than patients with high EPF. Such a finding agrees with the observation that the reductions of portal hepatic perfusion and of post-shunt portal pressure are independent predictors of overt hepatic encephalopathy in cirrhotic patients with selective splenorenal shunt (Spina, et al., 1993), and that a low portal pressure after TIPS is also associated with hepatic encephalopathy (Riggio et al., 1996). Moreover, it was suggested that surgical portal-systemic shunting worsens hepatic function because of the reduction of portal flow (Starzl, Porter, and Kashiwagi, 1975) which, in turn, impairs the clearance of substances highly extracted by the liver (Wilkinson and Shand, 1975) and reduces the amount of hepatotrophic factors carried to the hepatocytes by portal blood (Starzl, Porter, and Kashiwagi, 1975). The relationships, albeit weak, between EPF and serum bilirubin or Child-Pugh score are in accordance with the hypothesis that the reduction of portal flow yields a worsening in hepatic function. In actual fact, Kardel et al. (1975) and Galambos et al. (1976) found an association between the worsening of hepatic function and the occurrence of hepatic encephalopathy in cirrhotic patients who had undergone surgical portal-systemic shunt.

Another issue that should be taken into account is that the lower the EPF, the greater the portal-systemic blood shunting. Indeed, it has been well established that splanchnic inflow is not decreased, but increased, in cirrhosis (Piscaglia et al., 1998; Schrier et al., 1988). Therefore, a low hepatic portal perfusion yields not only a worsening of hepatic function, but also reflects a high degree of portal-systemic shunting. Consequently, it is difficult to separate the role of shunting and liver insufficiency in the pathophysiology of hepatic encephalopathy. The role of hepatocellular insufficiency in the pathophysiology of the early stages of cognitive dysfunction of patients with liver cirrhosis was emphasized by Kugler et al. (1994). The relationship between albumin, PT, and ammonia with S-EEG alterations in our study is in keeping with the importance of hepatocellular failure in the pathophysiology of CNSD in liver cirrhosis. However, in our study the role of portal hemodynamic alteration stands out and logistic multivariate regression analysis clearly showed that both impaired hepatocellular function (expressed by low prothrombin time) and low EPF were independent predictors of altered S-EEG, whereas only low EPF was an independent predictor of psychometric alterations. The importance of low hepatic portal

perfusion is also highlighted by the finding that it is a predictor of death in cirrhotic patients, both assessed semiquantitatively by the venous phase of mesenteric angiography (Finucci et al., 1991), and by Doppler sonography (Zoli et al., 1993). Because we found CNSD detected by psychometric test (Amodio et al., 1999a) or EEG (Amodio et al., 2001) to be a predictor of death in cirrhotic patients, it is possible to hypothesize that under a critical level of EPF at about 700 mL/min, the liver function declines so that the risk of hepatic encephalopathy and death substantially increases.

In conclusion, (1) for the first time low effective portal hepatic perfusion detected by DDU together with biochemical indices of hepatocellular failure was proved to be independently associated with minimal CNSD in cirrhotic patients; (2) the patency of the PUV *per se* was not associated with a higher prevalence of minimal central nervous system dysfunction in cirrhotic patients.

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