Relationship Between Cerebral Perfusion in Frontal–Limbic–Basal Ganglia Circuits and Neuropsychologic Impairment in Patients with Subclinical Hepatic Encephalopathy

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Early detection of neuropsychologic impairment in cirrhotic patients with subclinical hepatic encephalopathy (SHE) is important for their prognosis and quality of life. Abnormal MRI and MR spectroscopy (MRS) findings have been proposed as early markers of brain damage in these patients, but the role of functional neuroimaging in this field still has to be defined. In this study, the SPECT perfusion pattern in patients with SHE was investigated, and the relationship between regional cerebral blood flow (rCBF) and the MRI, MRS, neuropsychologic evaluation and biochemical data of these patients was assessed. **Methods:** Data were obtained from 13 cirrhotic patients with SHE and 13 age-matched healthy volunteers. Fasting venous blood ammonia and manganese sampling and a battery of standardized neuropsychologic tests related to basal ganglia function and sensitive to the effects of liver disease were all performed on the same day. MRI and ^{99m}Tc-hexamethyl propyleneamine oxime SPECT were performed within 2 wk. **Results:** A pattern of decreased prefrontal rCBF was found in patients with SHE compared with healthy volunteers. Basal ganglia and mesial temporal rCBF correlated inversely with performance on motor tasks involving speed (Purdue pegboard test) and frontal premotor function (Luria graphic alternances and Stroop tests). Thalamic rCBF correlated positively with T1-weighted MRI signal hyperintensity in the globus pallidus and with abnormal MRS findings. Neither the MRI signal intensity of the globus pallidus nor MRS correlated with neuropsychologic test results. **Conclusion:** Cirrhotic patients with SHE show a SPECT pattern of impaired prefrontal perfusion that does not seem to account for their neuropsychologic deficits. On the other hand, perfusion in some parts of the limbic system and limbic-connected brain regions, such as the striatum and the mesial temporal regions, increased with neuropsychologic impairment. These findings suggest that brain SPECT may be more sensitive than MRI in delineating cirrhotic patients requiring in-depth clinical testing to reveal basal ganglia–related neuropsychologic alterations.

Key Words: brain SPECT; subclinical hepatic encephalopathy; neuropsychology; MRI; MR spectroscopy

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Patients with liver cirrhosis and normal routine neurologic findings may present with characteristic neuropsychologic deficits. This clinical situation of latent or minimal encephalopathy is known as subclinical hepatic encephalopathy (SHE). The relatively selective impairment of complex attentional tasks, fine motor skills, and visuospatial perception in these patients has been reported to be an important cause of occupational and psychosocial morbidity (*1*). Thus, early detection of neuropsychologic involvement in cirrhotic patients without overt encephalopathy is important for their prognosis and quality of life. Although psychometric tests are commonly applied to detect cognitive dysfunction in these patients, little is known about the cerebral regions involved.

Research using both structural and functional neuroimaging techniques has been under way in an effort to find early markers of brain damage in patients with SHE (*2–15*). Structural neuroimaging abnormalities, such as an increased T1-weighted MRI signal intensity in the globus pallidus (*2–7*) and an MR spectroscopy (MRS) pattern of increased cerebral glutamine and decreased myoinositol and choline metabolites, have been described in cirrhotic patients without overt encephalopathy (*8–10*). Furthermore, a role for plasma ammonia and manganese has been proposed in the pathogenesis of the MRI findings (*11–15*).

Functional neuroimaging may help in defining the nature of these MRI abnormalities, but only a few studies reporting functional neuroimaging (i.e., PET or SPECT) findings in these patients have been published (*11*). This study was designed to investigate the SPECT perfusion pattern in nonencephalopathic cirrhotic patients and the relationship between regional cerebral blood flow (rCBF) and MRI pallidal hyperintensity, neurospectroscopy findings, neuropsychologic findings, and biochemical data in these patients.

MATERIALS AND METHODS

Patients

Thirteen consecutive outpatients with cirrhosis and SHE (6 women, 7 men; mean age [±SD], 62 ± 9 y; fully oriented and

without asterixis) were recruited. The cirrhosis was alcoholic in 3 patients and postnecrotic in 10. All patients had stable chronic liver disease, which was classified as Child class A (9 patients) or B (4 patients) but not C. All had evidence of portosystemic shunting, either spontaneous (proven esophageal varices) or surgically constructed. Consciousness was normal, as assessed by examination of mental status. Inclusion criteria also included no active alcoholism, nondecompensated medical conditions, no history of stroke, and informed consent. No patient had chronic pulmonary disease or abnormal respiratory conditions. For all patients, a low-protein diet (40–60 g protein per day) had been prescribed and brain SPECT, MRI, MRS, neuropsychologic testing, and biochemical analysis were performed within 2 wk. Thirteen age-matched healthy volunteers (5 women, 8 men; mean age, 58 ± 10 y) underwent brain SPECT for comparison. The study was approved by the ethics committee of Hospital de Sant Pau, and written informed consent was obtained from each subject.

Brain SPECT

The SPECT acquisition and reconstruction protocols were described elsewhere (*16*). A dual-head system (Elscint-Helix, Haifa, Israel), fitted with high-resolution collimators was used. Image acquisition started 20 min after intravenous injection of 740 MBq ^{99m}Tc-hexamethyl propyleneamine oxime (Nycomed Amersham, Madrid, Spain), using a 360° circular orbit, a step-and-shoot mode (a 20-s image every 3°), a 128 × 128 matrix, and an acquisition zoom of 1.5. The final pixel size was 2.96 mm. Full width at half maximum in the transaxial plane was 9 mm. Filtered backprojection was used for reconstruction by applying a Metz filter. Attenuation correction of the reconstructed data was applied using the Chang method, with a coefficient factor of 0.075. Quantitative analysis was performed to obtain region-to-reference ratios for each hemisphere. The cerebellum was selected as the reference region, because cerebellar abnormalities were not detected on either the SPECT images or the MR images. Irregular regions of interest (ROIs) previously stored in the computer as a template were placed by the same investigator, who was unaware of clinical data. Oblique slices 2 pixels thick and taken in the fronto-occipital direction were used to place ROIs corresponding to the cerebellum, orbitofrontal and prefrontal cortex, basal ganglia, and thalamus. Slices taken parallel to the long axis of the temporal lobe were used to place the lateral temporal and mesial temporal ROIs (Fig. 1). Mean counts per pixel on 2 consecutive slices were averaged for each region.

MRI Studies

MRI studies were performed using a 1.5-T Signa system (General Electric Medical Systems, Milwaukee, WI) and a quadrature head coil. MRS consisted of a pulse sequence obtained with the stimulated echo acquisition method (1600-ms repetition time, 20-ms echo time, 13.7-ms TM, 256 acquisitions, 2048 data points, and 2500-Hz spectral width), preceded by 3 chemical shift water-suppression pulses (50-Hz bandwidth). This pulse sequence was obtained with the single-voxel proton brain examination system (Probe/SV; General Electric), which automatically optimizes magnetic field homogeneity over the selected voxel and adjusts the water suppression pulses. Subjects were immobilized during MRS data acquisition, and no movement artifacts were detected. A single voxel placed in the globus pallidus (5.4 mL) was acquired in each subject. Small volumes were chosen to minimize partial-volume effects. Data were processed on a workstation (SPARCstation 20; Sun Microsystems, Mountain View, CA) using

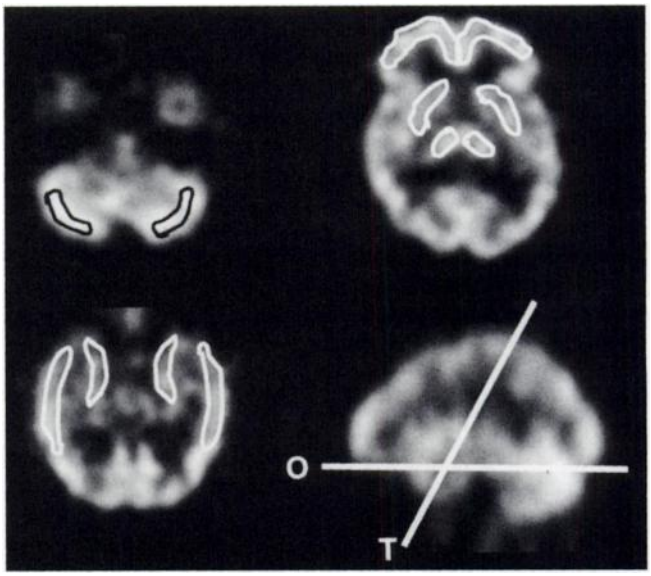

FIGURE 1. Representative template of ROIs used to obtain region-to-cerebellum SPECT ratios. ROIs corresponding to cerebellum, orbitofrontal and prefrontal cortex, basal ganglia, and thalamus were placed on orbitofrontal slices (O). ROIs corresponding to mesial and lateral temporal regions were placed on temporal slices (T).

a previously described method (*8*). Peak areas were estimated and results expressed as ratios, using creatine as a reference. Measurements were performed at the following resonances: N-acetylaspartate, 2.01 ppm; glutamine-plus, 2.15–2.50 ppm; creatine, 3.04 ppm; choline, 3.22 ppm; and myoinositol, 3.55 ppm. The ratio of glutamine to myoinositol plus choline was obtained as a representative measurement of the global metabolic abnormality in patients with liver disease.

MR images were obtained in the sagittal, axial, and oblique coronal planes. The signal intensity of the globus pallidus was measured on 35-mm^2 ROIs in a single slice of the oblique coronal projection obtained from an inversion-recovery sequence (1500-ms repetition time, 20-ms echo time, 650-ms inversion time, 22-cm field of view, 256 × 192 pixel matrix, 5-mm slice thickness, and 1.5-mm interslice gap). The method of measurement, which has been described previously (*4*), involved measurement of the globus pallidus signal intensity normalized to the putamen signal intensity using the signal intensity ratio of the globus pallidus minus the putamen to the globus pallidus plus the putamen.

To establish the value of the signal intensity ratio in a control group, we used data from 37 healthy volunteers (15 women, 22 men; mean age, 59.6 ± 22 y) (*4*). The mean signal measurement from this group was 0.04 ± 0.03. With mean ± 2 SDs considered the statistical criterion for a normal range, values higher than 0.10, indicating increased signal in the globus pallidus, were considered abnormal.

Neuropsychologic Tests

For neuropsychologic evaluation, we selected standardized tests related to basal ganglia function and sensitive to cerebral dysfunction in cirrhotic patients without overt encephalopathy. Using a previously described method (*4,7*), we chose the Purdue pegboard test to evaluate motor function and speed, the Luria graphic and motor alternances test to evaluate premotor function, and the Stroop test to evaluate complex attentional skills (*17*).

Biochemical Data

All studies were performed in the same laboratory, with immediate analysis of blood samples for plasma ammonia levels (normal range, 12–47 μmol/L), differential counts, and routine chemistry. Whole-blood manganese assays were performed in a specialized toxicologic laboratory using furnace graphite atomic absorption spectroscopy and were verified by repetition (with a validated upper value for manganese of 3.1 μg/L in healthy adults). All blood samples were collected identically, and no clinical information was provided to the laboratory. Plasma ammonia and blood manganese levels were obtained for statistical purposes.

Statistics

Student's *t* test was applied to independent samples for comparison of rCBF ratios between cirrhotic patients and healthy volunteers. The Pearson product moment correlation was used to analyze rCBF ratios, MRI signal intensity from the globus pallidus, MRS findings, neuropsychologic scores, and blood ammonia and manganese levels. The results are shown without correction for multiple comparisons to emphasize the patterns of correlations found.

RESULTS

SPECT Perfusion Pattern

Region-to-cerebellum ratios obtained from cirrhotic patients differed from those obtained from healthy volunteers only in the left prefrontal region, which was hypoperfused in cirrhotic patients (90.3 ± 7.0 in cirrhotic patients versus 96.2 ± 3.5 in healthy volunteers, $P = 0.012$). Differences in mean regional perfusion ratios in basal ganglia between patients and healthy volunteers did not reach statistical significance, even when the subgroup of patients with the poorer neuropsychologic performance was subsequently compared with the healthy volunteers.

MRI Studies

The mean signal intensity of the globus pallidus in patients measured 0.13 ± 0.04 contrast units. In 8 of the 13 patients, the measurement was outside normal limits. Spectroscopic analysis of the globus pallidus showed an increase in the ratio of glutamine-plus to creatine and a reduction in the ratios of myoinositol to creatine and choline to creatine (Table 1). Ratios outside normal limits were seen for glutamine-plus to creatine in 11 patients, for myoinositol to creatine in 13, and for choline to creatine in 6. No or mild cortical atrophy (n = 4) was observed in these patients. No correlations were found between MRI data and neuropsychologic performance.

TABLE 1
Comparison of MR Spectroscopy Ratios Between Healthy Volunteers and Patients with SHE

Parameter	Healthy volunteers (n = 13)	Patients (n = 13)	P*
mI/Cr	0.54 ± 0.13	0.33 ± 0.23	<0.001
Cho/Cr	0.78 ± 0.11	0.69 ± 0.21	<0.005
Glx/Cr	1.19 ± 0.24	1.68 ± 0.69	<0.001
NAA/Cr	1.13 ± 0.12	1.08 ± 0.20	NS

*Student *t* test.
mI = myoinositol; Cr = creatine; Cho = choline; Glx = glutamine-plus; NAA = N-acetylaspartate; NS = not statistically significant.

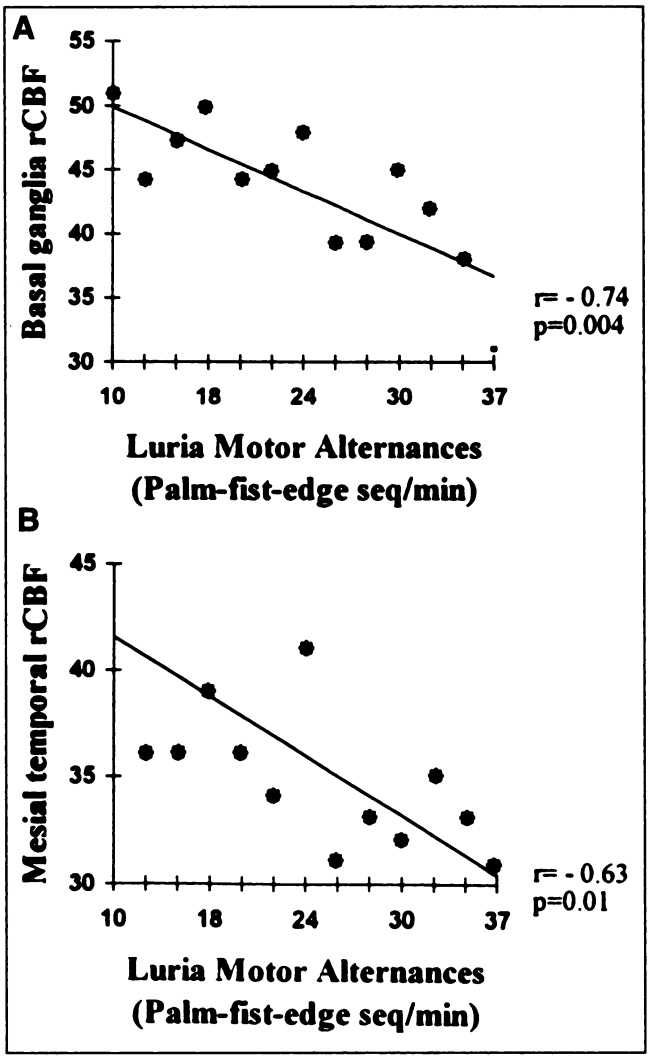

FIGURE 2. Correlation between basal ganglia (A) and mesial temporal (B) rCBF and number of palm–fist–edge sequences performed in 1 min on Luria motor alternances test (n = 13).

Relationship Between SPECT Findings and Other Findings

The only correlation found between rCBF and the MRI pallidal signal was in the thalamus ($r = 0.60$; $P = 0.03$). The thalamus was also the only structure showing a correlation between the rCBF ratio and the MRS ratio (glutamine to myoinositol plus choline) ($r = 0.75$; $P = 0.003$).

The striatum and the mesial temporal rCBF correlated with measures of premotor function, with motor function and speed, and with the complex attentional task. The fewer the palm–fist–edge sequences performed by a patient in 1 min (Fig. 2), the higher the perfusion in these regions. Likewise, placing fewer pegs in pegboard during a 30-s trial (Fig. 3) and making more errors while completing complex attentional tasks (Fig. 4) were associated with higher

perfusion in these regions. Figure 5 shows a representative rCBF pattern from a patient with poor neuropsychologic performance.

The mean plasma ammonia level in patients was 59.5 ± 32.7 μmol/L. In 7 patients, the levels were above normal. A significant correlation between SPECT data and plasma ammonia levels was found for the mesial temporal region (r = 0.66; P = 0.01). The mean blood manganese level in patients was 1.90 ± 0.32 μg/L. In no patient was the value outside normal limits. No statistically significant correlations were found between blood manganese levels and signal intensity in the MRI globus pallidus, MRS or SPECT findings, or neuropsychologic data.

DISCUSSION

This study focused on cerebral perfusion SPECT patterns in cirrhotic patients with SHE. An impaired prefrontal blood flow was found when comparing patients with age-matched healthy volunteers. Thalamic rCBF correlated positively with MRI and MRS data. Poor neuropsychologic performance correlated significantly with high perfusion in limbic and limbic-connected brain regions, such as the striatum and the mesial temporal region, whereas no relationship was found between MRI or MRS data and neuropsychologic performance. These findings contribute to the growing evidence of early cerebral functional abnormalities in cirrhotic patients without overt encephalopathy.

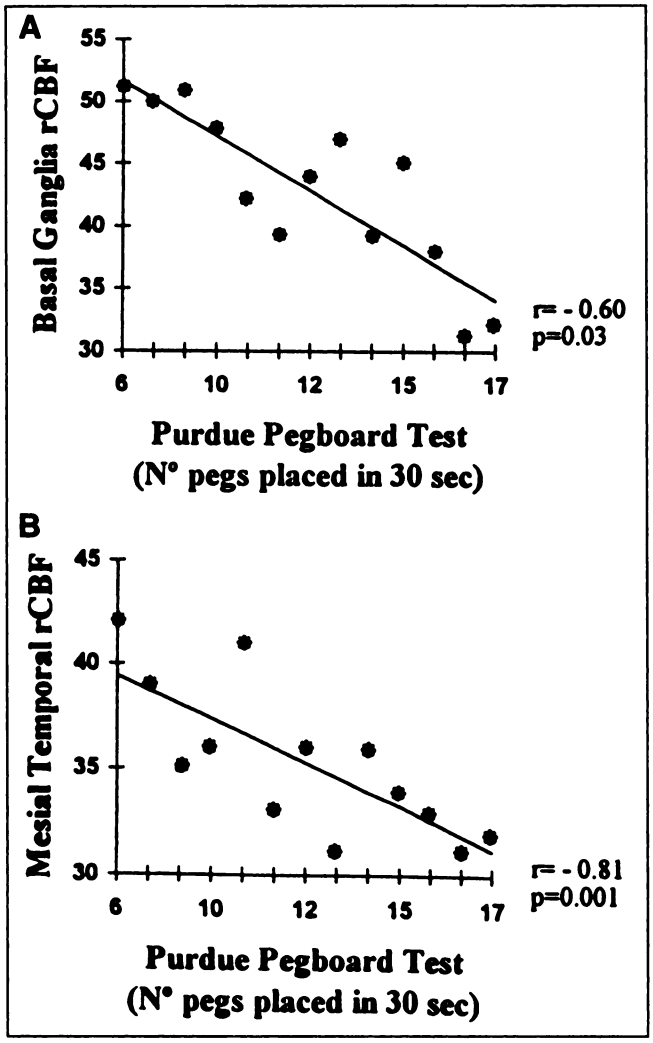

FIGURE 3. Correlation between basal ganglia (A) and mesial temporal (B) rCBF and number of pegs placed in pegboard in 30-s trial on Purdue pegboard test (n = 13).

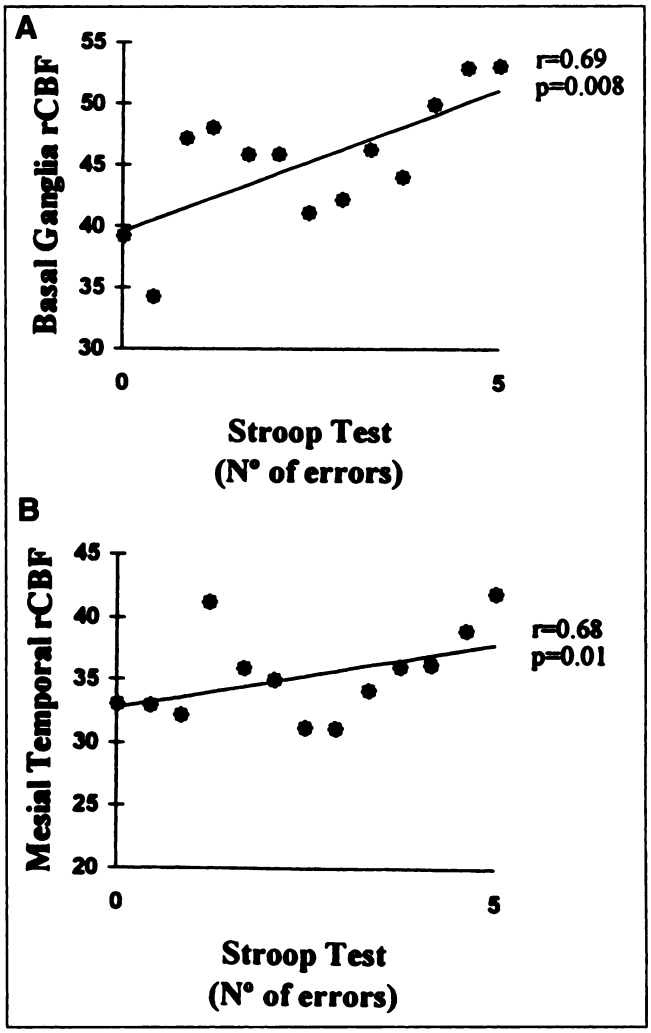

FIGURE 4. Correlation between basal ganglia (A) and mesial temporal (B) rCBF and number of errors performed on Stroop test (n = 13).

SPECT Perfusion Pattern in Patients with SHE

Widespread rCBF impairment in several regions has been reported in patients with encephalopathy and cirrhosis compared with healthy volunteers (*18–22*), with the frontal cortex and the basal ganglia being the most consistently involved. Our patient sample showed a statistically significant rCBF decrease in the left prefrontal cortex in comparison with healthy age-matched volunteers. Impaired flow and oxygen metabolism in the frontal cortices and the anterior cingulate gyrus in cirrhotic patients have also been reported by other groups (*20–22*). In this study the anterior cingulate

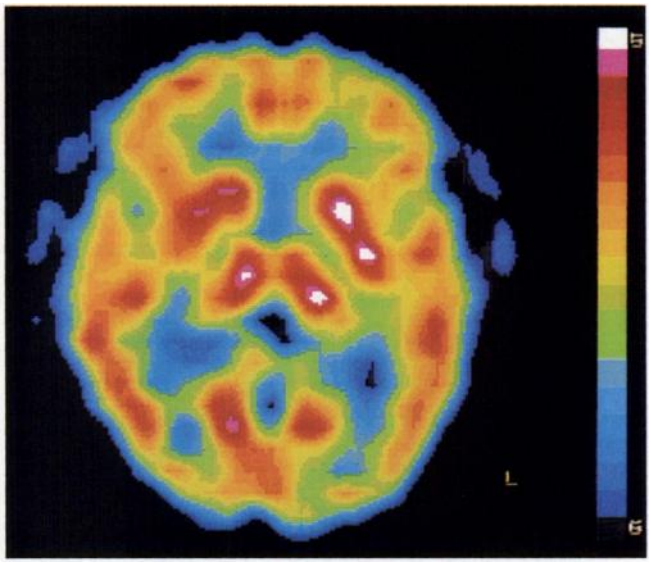

FIGURE 5. Representative SPECT slice at basal ganglia level from patient with SHE and poor neuropsychologic performance shows high activity in basal ganglia and thalamus and mild left prefrontal hypoperfusion.

gyrus was included in the prefrontal ROI and, therefore, was not independently evaluated. The frontal rCBF impairment present in these patients may account for the relatively selective deficits in attentional mechanisms, but this hypothesis has rarely been examined. Trepacz et al. (*22*) found a statistically significant correlation between frontotemporal rCBF impairment and defects in executive abilities, visual memory, and visuomotor skills in patients with subclinical encephalopathy. In this study, prefrontal rCBF did not correlate with motor, premotor, or attentional cognitive functions, but differences in the battery of tests used to study it should be considered. Cerebral atrophy, which may be present even in cirrhotic patients who are in a stable nonencephalopathic state, should also be considered when interpreting frontal rCBF impairment, because the increase in spaces containing cerebrospinal fluid can contribute to the decrease in rCBF values (*23*). However, the relatively few patients exhibiting this finding in our study reduces the probability that atrophy itself could explain the frontal rCBF impairment.

A pattern of increased blood flow and metabolism in basal ganglia has also been reported in cirrhotic patients with several degrees of encephalopathy (*18,20,24*). In this study, patients who performed poorly during neuropsychologic tests had the highest perfusion ratios in basal ganglia, but mean rCBF ratios were not significantly higher in patients with SHE than in healthy volunteers. However, the inverse correlation found between basal ganglia rCBF and neuropsychologic performance is consistent with the increased rCBF in basal ganglia reported by other authors.

Relationship Between SPECT Findings and Other Findings

In this study, the thalamus was the only structure correlating with both MRI pallidal signal and MRS measurement (the higher the thalamic rCBF, the more evident the abnormal MRI and MRS findings). Interestingly, neither the thalamic rCBF, the MRI pallidal signal, nor the MRS measurement correlated with the neuropsychologic scores obtained in our sample. Although no single metabolic derangement accounts for hepatic encephalopathy, the most replicated biochemical factor, among all that can be related to SHE, has been plasma ammonia (*1,4*). The MRI pallidal signal has been related to ammonia (*4*). However, the lack of correlation between plasma ammonia levels and thalamic rCBF seems to rule out the possibility that ammonia influences thalamic perfusion. Some investigators have suggested that the globus pallidus hyperintensity may be caused by pathologic accumulation of certain metabolites such as manganese in patients with chronic liver failure (*12–14*), who have increased plasma levels of these substances because of metabolic failure. This situation would cause neurodegeneration in the globus pallidus. However, our data do not favor a quantitative relationship between blood manganese levels and rCBF or MRI signal hyperintensity in the globus pallidus in stable cirrhotic patients. Besides manganese, several other substances, including metals (e.g., copper and zinc) are conveyed by the portosystemic shunt created by chronic hepatic disease and may accumulate in the brain. In fact, 50% more than the normal concentrations of manganese and copper were found in autopsy samples of the globus pallidus and putamen from 3 patients with hepatic cirrhosis (*14*). Notably, imaging changes during life appear in the globus pallidus and not in the caudate nucleus, which has the highest postmortem manganese level (*12,13*). Moreover, in 3 of 19 cirrhotic patients (15.8%), the MRI appearance of the globus pallidus after 2 y of follow-up was normalized without liver transplantation or diet modifications influencing manganese (*7*). Thus, more research is needed to confirm a cause-and-effect relationship between manganese accumulation in the basal ganglia, chronic hepatic encephalopathy, MRI globus pallidus hyperintensity, and brain perfusion.

Present concepts about the functional organization of the basal ganglia are based on anatomically shown multiple parallel loops of signal flow from the cortex through the basal ganglia and back to the cortex (*25*). The putaminal, caudate, and pallidal nuclei form the main outputs for the motor and complex cognitive circuits of the basal ganglia. Through their projections to the thalamus, they are assumed to influence restricted portions of the frontal lobe (*25*). In addition to input from the cortex and thalamus, the striatum also receives projections from the nuclei of the dorsal raphe, the locus caeruleus, and the amygdala (*26*). Presumably, these inputs also serve to modify transfer of information through the various basal ganglia–thalamocortex circuits, including the frontal–limbic–basal ganglia circuits (*25*). We hypothesize that basal ganglia dysfunction, whatever the cause, leads to disinhibition of thalamic activity, which is reflected in SPECT as hyperperfusion and therefore suggests a role for the striatal–thalamic loop in the pathophysiology

of pallidal hyperintensity on MRI. This point is another adding to the growing evidence that such abnormal MRI findings are of functional rather than structural origin. In this study, rCBF in the basal ganglia and the mesial temporal region related to neuropsychologic performance. Some parts of the limbic system, such as the hippocampus, the parahippocampal gyrus, and the amygdala (*27*), were included in the mesial temporal ROI. Interconnections between the limbic system and the striatum (*25,27*) may account for the similar rCBF pattern found in the basal ganglia and mesial temporal regions. The higher the perfusion in these regions, the poorer the test performance. This finding is consistent with the negative correlation between basal ganglia rCBF and cognitive impairment reported by O'Carroll et al. (*20*). This perfusion increase in the limbic circuit may be the result of a compensatory response to premotor, motor, and complex attentional deficits.

Mesial temporal rCBF correlated positively with plasma ammonia levels, but no correlation was found between plasma ammonia levels and neuropsychologic testing. Passage of ammonia into the brain seems to be facilitated in patients with cirrhosis (*18*). However, a correlation is not always found because plasma ammonia levels vary greatly (*7*). Further research is still needed to clarify the role of plasma ammonia in the pathogenesis of functional and metabolic cerebral abnormalities in patients with SHE.

CONCLUSION

Cirrhotic patients with SHE show a SPECT pattern of impaired prefrontal perfusion that does not seem to account for their neuropsychologic deficits. On the other hand, perfusion in the striatum and mesial temporal regions, including some parts of the frontal–limbic–basal ganglia circuits, increases with neuropsychologic impairment. Therefore, brain perfusion appears more directly associated with the selective deficits in complex attentional and fine motor skills seen in these patients. These findings suggest that brain SPECT may be more sensitive than MRI in delineating those cirrhotic patients requiring in-depth clinical testing to reveal basal ganglia–related neuropsychologic alterations. The relationship found between thalamic rCBF, MRI pallidal signal, and MRS pattern supports the hypothesis of a functional rather than a structural origin for the MRI pallidal hyperintensity and suggests a role for the frontal–limbic–basal ganglia circuits in the pathophysiology of such abnormalities. Finally, the disparity of results found with the MRI pallidal signal and rCBF suggests that brain SPECT and MRI abnormalities reflect different aspects of neuropsychologic involvement in cirrhotic patients with SHE.

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