Brain Perfusion Single Photon Emission Computed Tomography Abnormalities in Patients with Minimal Hepatic Encephalopathy

Hejjaji Venkataramarao Sunil*, Bhagwant Rai Mittal*, Roshan Kurmi**, Yogesh K Chawla**, Radha K Dhiman**

Departments of *Nuclear Medicine and **Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India

Background: Minimal hepatic encephalopathy (MHE) is the mildest form of hepatic encephalopathy (HE). Minimal hepatic encephalopathy patients do not demonstrate clinically overt symptoms of HE but present with abnormal neuropsychological and/or neurophysiological tests indicative of cerebral dysfunction. This study was performed in such patients to identify regions of abnormal cerebral perfusion and to correlate regional cerebral blood flow (rCBF) changes with psychometric hepatic encephalopathy score (PHES), Child–Turcotte–Pugh’s score (CTP), and model for end-stage liver disease (MELD) score. We also compared abnormal patterns of rCBF in cirrhotic patients of alcoholic etiology with non-alcoholic etiology. **Methods:** This prospective study was performed to evaluate rCBF in 50 cirrhotic patients and 13 controls using technetium-99m ethyl cysteinate dimer (Tc-99m ECD) brain single photon emission computed tomography. All the patients underwent a battery of psychometry tests, PHES. Minimal hepatic encephalopathy was diagnosed if PHES was ≤ -5 . The rCBF changes were evaluated using region of interest (ROI) based semi-quantitative method of region/cerebellum and region/cortex ratios in 16 regions of the brain. **Results:** Cirrhotic patients with MHE showed impaired perfusion in the superior prefrontal cortex and increased perfusion in the thalamus, brain-stem, medial temporal cortex, and the hippocampus when compared with the controls. Cerebral perfusion in superior prefrontal cortex correlated negatively with MELD score ($r = -0.323$, $P = 0.022$). We found significant positive correlation between PHES score and rCBF values in the left superior prefrontal cortex ($r = 0.385$, $P = 0.006$). Cirrhotic patients with alcohol etiology showed significantly decreased rCBF in right inferior prefrontal cortex, right superior prefrontal cortex, and the anterior cingulate cortex while increased rCBF was noted in the right medial temporal cortex and hippocampus. **Conclusion:** Our results suggest that alterations in cognition in cirrhotic patients with MHE may be associated with impaired abnormalities of rCBF. (J CLIN EXP HEPATOL 2012;2:116–121)

Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of other known brain diseases. Minimal HE (MHE) was a term proposed to identify patients with subtle manifestations of HE that are difficult to recognize.^{1,2} The prevalence of MHE is estimated to vary from 30% to 84% according to

studies using different methods.^{3,4} Early detection of MHE is clinically relevant for several reasons. Minimal hepatic encephalopathy impairs daily functioning and health-related quality of life (HRQOL),^{5,6} it predicts the development of overt HE,^{7,8} it is associated with poor prognosis,^{9,10} and these patients experience higher rates of accidents, driving problems, and falls.^{11–14} Furthermore, treatment with lactulose or rifaximin improves cognitive functions as well as HRQOL and driving simulator performance in these patients.^{6,15,16}

Neuropsychological tests are commonly applied to detect MHE in patients with liver cirrhosis,⁵ but they provide no information about the cerebral regions involved. Many studies using brain perfusion single photon emission computed tomography (SPECT) have highlighted the presence of perfusion defects in various parts of the brain and have correlated these findings with neurophysiological parameters as well as clinical status.^{17–23} This prospective study was conducted to evaluate the role of SPECT in recognizing regional cerebral blood flow (rCBF) changes in a group of stable cirrhotic patients with MHE.

Keywords: Brain SPECT, cirrhosis liver, MHE, rCBF, Tc-99m ECD

Received: 11.01.2012; **Accepted:** 17.06.2012

Address for correspondence: Bhagwant Rai Mittal, Professor and Head, Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India

E-mail: brmittal@yahoo.com

Abbreviations: CI: confidence interval; CTP: Child–Turcotte–Pugh’s score; FCT-A: figure connection test; HE: hepatic encephalopathy; HRQOL: health-related quality of life; MELD: model for end-stage liver disease; MHE: Minimal hepatic encephalopathy; MMSE: mini mental state examination; NCT: number connection test; PHES: psychometric hepatic encephalopathy score; rCBF: regional cerebral blood flow; ROI: region of interest; SPECT: single photon emission computed tomography; Tc-99m ECD: technetium-99m ethyl cysteinate dimer

doi: 10.1016/S0973-6883(12)60099-1

METHODS

Fifty consecutive patients with cirrhosis of liver were prospectively enrolled into the study. Cirrhotic patients who did not demonstrate clinically overt symptoms of HE, but had abnormal neuropsychological tests indicative of cerebral dysfunction were defined as having MHE.

Exclusion criteria were overt HE or a history of overt HE; history of recent (<3 months) alcohol intake; infection or antibiotic use, recent (<6 weeks); gastrointestinal bleeding; history of recent (<6 weeks) use of drugs affecting psychometric performances like benzodiazepines, antiepileptic, and psychotropic drugs; history of shunt surgery or transjugular intrahepatic portosystemic shunt for portal hypertension; electrolyte imbalance; renal impairment; presence of hepatocellular carcinoma; severe medical problems such as congestive heart failure, pulmonary disease, neurological or psychiatric disorder, etc. that could influence performance of neurophysiologic tests. Patients below 18 years and above 70 years of age, pregnant women, and patients with ear abnormalities were excluded from the study.

All the subjects enrolled in the study underwent routine clinical examination/clinical investigations, psychometric hepatic encephalopathy score (PHES), and brain SPECT study. Clinical examination included a thorough general physical and systemic examination including complete neurological and mental state examination using mini mental state examination (MMSE) to exclude the presence of any illness, which can cause or affect the neurological status. West Haven Criteria for grading mental state was used for grading HE.² Mini mental state examination was performed to exclude overt cognitive impairment in all patients before formal test(s) for the diagnosis of MHE was administered; a score of 23 or lower was indicative of cognitive impairment and clinically overt HE.⁵ Laboratory investigations included a complete hemogram, serum electrolytes, renal and liver function tests, and complete coagulogram. Upper gastrointestinal endoscopy was performed in all patients for the presence of esophageal varices and the severity of liver disease was determined by CTP and MELD scores.

Psychometric Hepatic Encephalopathy Score

Psychometric hepatic encephalopathy score contains 6 tests—number connection test (NCT)-A, NCT-B, serial dotting test, digit symbol test, line tracing test for time (*t*), and for error (*e*).²⁴ In Indian version we replaced NCT-B with figure connection test (FCT-A) because of concerns that some of our patients were not familiar with English alphabets and could not perform NCT B. In principle, the FCT is similar to the NCT, except that numbers are replaced by figures (motifs).²⁵ Figure connection test is a universally applicable test to assess mental state, which transcends the barriers of linguistic differences and illiteracy.²⁵ The

clinical significance of PHES has been evaluated in a large number of healthy volunteers and patients with MHE.⁹

Diagnosis of Minimal Hepatic Encephalopathy

In Indian patients PHES ≤ -5 was considered abnormal and was diagnostic of MHE.⁹

Brain Perfusion Single Photon Emission Computed Tomography

To evaluate rCBF, the SPECT study was performed in all patients after obtaining informed written consent and using technetium-99m ethyl cysteinate dimer (Tc-99m ECD); 20 mCi of the radiopharmaceutical was injected intravenously in a calm dark room through a venous canula fixed about 30 minutes prior to the injection. Imaging was done 40 minutes later under a dual-headed gamma camera (E. Cam; Siemens, Erlangen, Germany) coupled with high-resolution general-purpose collimator. Data were acquired in 128 $\times$ 128 matrix over 360° rotation acquiring 64 frames, each frame of 20 s duration. Reconstruction of the data was done by a single operator in all the patients, in transaxial, coronal, and sagittal planes. A Butterworth filter of order 10, cut-off 0.45 and Chang's attenuation correction were applied. Semi-quantitative analysis of the Tc-99m ECD uptake was performed using the region of interest (ROI) templates.¹⁰ Region of interest templates were drawn on paired regions of both cerebral cortices and unpaired regions in the mid-sagittal image. Mean counts in each ROI of the SPECT image is influenced by various factors, like dose of the tracer injected and time of acquisition from the time of injection. Hence, to quantify regional Tc-99m ECD uptake, the mean counts in each selected region was normalized with respect to the mean counts in the cerebellum (region-to-cerebellum ratio) and in the cerebral cortex (region-to-cerebral cortex ratio). The mean count in the cerebral cortex was obtained by averaging the counts in all ROIs in the cerebral cortex, excluding the anterior and posterior cingulate cortex, and the brain stem. The data of cirrhotic patients with or without MHE was compared with each other and with normal database of Tc-99m ECD SPECT of 13 healthy controls. The median of mean/cerebellum and mean/cortex of each region was determined.

Statistical Analysis

Data were expressed as mean or median with 95% confidence interval (CI) and proportions with percentage where appropriate. For normally distributed data ANOVA was used, and for skewed data Mann-Whitney test was used. Statistical analyzes for the categorical data were performed using χ^2 test or Fisher's exact test. The relationships between rCBF and PHES, and CTP and MELD scores were assessed by Spearman-Rho rank correlation coefficient. The probability level of $P < 0.05$ was set for statistical significance.

Statistical analysis was performed with SPSS software for Windows, version 10.0 (SPSS Inc., Chicago, IL).

RESULTS

Fifty patients (41 men, 9 women; mean age 46.5 years) with cirrhosis of liver and 13 age-matched controls (7 men, 6 women; mean age 44.3 years) were included in the study. The causes of the patients' cirrhosis included alcohol abuse in 27 patients, chronic viral hepatitis in 8 patients (HBV 3 patients, HCV 4 patients, HBV+HCV 1 patient), and other causes in 15 patients (autoimmune hepatitis-4, non-alcoholic steatohepatitis-2, primary biliary cirrhosis-2, primary sclerosing cholangitis-1, and cryptogenic cirrhosis-6). Alcoholic patients were all males and had higher CTP scores ($P=0.026$) indicating more severe derangement of hepatic function. Minimal hepatic encephalopathy patients showed a lower mean corrected PHES score than the non-MHE group ($P=0.001$). No difference was found in the PHES scores between alcoholics and non-alcoholics ($P=0.344$). The demographic features and clinical profile of MHE and non-MHE patients are depicted in Table 1.

Brain Perfusion Single Photon Emission Computed Tomography

In all patients, significantly decreased uptake of Tc-99m ECD was found in parietal cortex and left superior prefrontal cortex compared to control group, indicating impaired blood flow to cerebral regions subserving cognitive functions (Table 2). Other areas showed no differences between patients and controls. Patients with MHE compared with controls showed significant decreased uptake in left superior prefrontal cortex. Patients without MHE compared with controls showed decreased uptake in right parietal cortex. These findings indicate that patients with cirrhosis of liver even without MHE have deficits in rCBF, which may account for disturbances in memory and neurophysiological tests for integrity of polysynaptic pathways involving the brain stem. Cirrhotic patients also showed increased uptake of Tc-99m ECD in right caudate, left thalamus, brain stem, bilateral medial temporal cortex, and hippocampus indicating increased neuronal activity in GABAergic inhibitory neurons of the basal ganglia.

Table 1 Demographic and clinical profile of patients with and without minimal hepatic encephalopathy.

Parameter	MHE (n=22)	Non-MHE (n=28)	P value
Age (yr±SD)	47.68 (±11.038)	45.50 (±12.627)	0.550
Sex			
Male	18 (81.8%)*	23 (82.1%)*	0.976
Female	4 (18.2%)*	5 (17.9%)*	
Etiology			
Alcohol	11 (50%)*	16 (57.1%)*	0.615
Non-alcohol	11 (50%)*	12 (42.9%)*	
Education (yr±SD)	8.09 (±4.566)	11.61 (±4.693)	0.008
Bilirubin (mg/dL)	2.488 (1.703–3.272) [†]	2.468 (1.656–3.279) [†]	0.732
AST (IU/L)	92.27 (64.11–120.44) [†]	70.64 (59.31–81.97) [†]	0.451
ALT (IU/L)	102.09 (23.10–181.09) [†]	52.43 (42.45–62.41) [†]	0.218
Albumin (g/dL)	2.959 (2.677–3.241) [†]	3.411 (3.164–3.657) [†]	0.011
Prolongation in PT (s)	3.73 (2.47–4.98) [†]	3.86 (2.03–5.68) [†]	0.466
INR	1.3300 (1.1981–1.4619) [†]	1.3800 (1.1672–1.5928) [†]	0.530
Ascites			
Yes	10 (47.6%)*	10 (35.7%)*	0.401
No	11 (52.4%)*	18 (64.3%)*	
Varices			
Yes	14 (63.6%)*	16 (57.1%)*	0.642
No	8 (36.4%)*	12 (42.9%)*	
CTP class			
A	4 (18.2%)*	9 (32.1%)*	0.478
B	13 (59.1%)*	15 (53.6%)*	
C	5 (22.7%)*	4 (14.3%)*	
CTP score	8.18 (7.40–8.96) [†]	7.29(6.63–7.94) [†]	0.062
MELD score	11.18 (9.23–13.13) [†]	11.25 (8.87–13.63) [†]	0.906
PHES score	−8.95 (−10.25–7.66)	−1.32 (−2.07 to −0.57)	0.000

*Number (percentage); [†]mean, (95% confidence interval).

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTP: Child–Turcotte–Pugh; INR: international normalization ratio; MELD: model of end-stage liver disease; MHE: minimal hepatic encephalopathy; PT: prothrombin time.

Table 2 Comparison of regional cerebral blood flow data of patients and controls.

Region	Ratio	Patients (n=50)	Controls (n=13)	P value
Caudate	Right/cortex	1.16510 (1.15420–1.18394)	1.14750 (1.03240–1.17263)	0.027
Thalamus	Mean/cortex	1.10766 (1.08762–1.12609)	1.07282 (1.03136–1.10343)	0.038
	Left/cortex	1.10536 (1.08064–1.12047)	1.06646 (0.96653–1.11034)	0.047
Superior prefrontal	Mean/cortex	0.95279 (0.94919–0.97866)	0.97841 (0.96906–1.00759)	0.000
	Left/cortex	0.95288 (0.94192–0.98348)	0.97989 (0.90893–1.01538)	0.030
Parietal cortex	Mean/cortex	0.96640 (0.94915–0.97651)	0.99542 (0.96774–1.04875)	0.026
Brain stem	Mean/cortex	0.96378 (0.95423–0.99047)	0.92510 (0.83327–0.95680)	0.007

Results given as median (95% confidence interval).

Cirrhotic patients with MHE compared with non-MHE group showed significantly decreased uptake in left superior prefrontal cortex. Increased uptake of tracer was noticed in bilateral thalamus and right parietal cortex. These findings of increased neuronal activity in basal ganglia and visual association areas may account for some of the motor manifestations and deficits in visuo-motor tasks in patients with MHE.

Significantly decreased uptake was found in right inferior prefrontal cortex, right superior prefrontal cortex, and the anterior cingulate cortex in alcoholic patients compared to non-alcoholics. These alterations may be attributed to toxic effects of alcohol. Altered rCBF in the above-mentioned regions may account for deficits in memory, attention, and other cognitive functions. Alcoholic patients also showed increased uptake in right medial temporal cortex and hippocampus.

Correlation between Regional Cerebral Blood Flow and Psychometric Hepatic Encephalopathy Score, Child–Turcotte–Pugh’s Score and Model for End-stage Liver Disease Score

Psychometric hepatic encephalopathy score correlated positively with left superior prefrontal cortex ($r=0.385$, $P=0.006$). Child–Turcotte–Pugh’s score correlated negatively with right inferior prefrontal cortex ($r=-0.415$, $P=0.003$), and left sensorimotor cortex ($r=-0.355$, $P=0.011$). Positive correlation was found between CTP score and uptake in left medial temporal cortex and hippocampus ($r=0.386$, $P=0.006$). Model for end-stage liver disease score correlated negatively with right superior prefrontal cortex ($r=-0.323$, $P=0.022$) and right lateral temporal cortex ($r=-0.347$, $P=0.014$) (Table 3).

DISCUSSION

Early diagnosis and treatment of MHE is important for several reasons. Minimal hepatic encephalopathy predicts subsequent development of overt HE. There is a scope to treat these patients at an early stage and prevent further deterioration of cognitive status. The prevalence of MHE in this study was 44% in cirrhotics, which is similar to earlier reports from the same population.^{6,8,26} The study also

emphasized the high prevalence of alterations of PHES in cirrhotic patients without overt HE. There was no statistically significant difference in the prevalence of MHE in the alcoholic and non-alcoholic groups.

Attention deficits are the main components of MHE. Main components of the spatial attentional network are the posterior parietal cortex, the dorsolateral prefrontal cortex, and the cingulate gyrus.²⁷ Alterations in rCBF in these regions of cerebral cortex may be the basis for deficits in memory and cognitive function in patient with MHE.

In the present study decreased perfusion was noticed in the left superior prefrontal cortex and bilateral parietal cortex. Reduced perfusion in frontal and parietal cortices in cirrhotic patients has been previously reported by Nakagawa et al²¹ who used statistical parametric mapping method for analyzing their Tc-99m ECD brain SPECT data. A comparison of rCBF between 13 cirrhotics and 13 controls by Catafau et al showed increased perfusion in striatum and medial temporal cortex.²⁸ Our results showed a statistically significant decrease in the rCBF in left superior prefrontal cortex and increase in thalamus and right parietal cortex in the MHE patients as compared with the cirrhotic patients without MHE. Deficits in attention due to reduced rCBF in superior prefrontal cortex may explain impaired performance of MHE patients in neuropsychological tests. It also explains deficits demonstrated by MHE patients in day-to-day activities like fitness to drive, memory, and concentration. Our findings are in accordance with previous studies documenting decreased rCBF in superior prefrontal cortex in patients with MHE.

Evaluation of blood flow in the anterior cingulate gyrus has been reported by Iwasa et al²⁰ as a simple and good indicator of cerebral function changes in patients with liver cirrhosis. Anterior cingulate gyrus mediates attention, target analysis, and response formulation. Decreased rCBF in anterior cingulate has been used to specifically differentiate cirrhotic patients with and without MHE. We did not find statistically significant difference in the anterior cingulate blood flow between MHE and non-MHE groups. However, in our study alcoholic patients when compared with the non-alcoholics showed reduced perfusion in anterior cingulate cortex, superior and inferior prefrontal cortices, and an increased perfusion in

Table 3 Correlation of regional cerebral blood flow with psychometric hepatic encephalopathy score and Child–Turcotte–Pugh and model of end-stage liver disease scores.

Region	Ratio	PHES score (r^*)	CTP score (r^*)	MELD score (r^*)
Inferior prefrontal cortex	Right/cerebellum	0.094	–0.304**	–0.186
	Mean/cortex	0.162	–0.302**	–0.153
	Right/cortex	0.136	–0.415(†)	–0.255
Broca's cortex	Left/cortex	0.198	–0.196	–0.044
	Mean/cortex	0.126	–0.233	–0.103
	Right/cortex	0.145	–0.264	–0.161
Superior prefrontal cortex	Mean/cortex	0.376†	–0.268	–0.219
	Right/cortex	0.232	–0.220	–0.323**
	Left/cortex	0.385†	–0.178	–0.045
Sensory motor cortex	Mean/cortex	0.147	–0.319**	–0.087
	Left/cortex	0.135	–0.355**	–0.053
Lateral temporal cortex	Right/cortex	0.174	–0.167	–0.347**
Medial temporal and hippocampus	Left/cerebellum	–0.213	0.281**	0.134
	Mean/cortex	–0.210	0.375†	0.182
	Left/cortex	–0.272	0.386†	0.191

*Spearman-Rho rank correlation coefficient; **correlation is significant at the 0.05 level (2-tailed); †correlation is significant at the 0.01 level (2-tailed).

CTP: Child–Turcotte–Pugh score; MELD: model of end-stage liver disease; PHES: psychometric hepatic encephalopathy score.

bilateral medial temporal cortex and the hippocampus, which may be attributable to such toxic effects of alcohol.

Increased rCBF in right parietal cortex in our study is in contrast to some of the previous studies that have reported reduced rCBF in the same region.^{18,21,29} These contradictory results in rCBF values in right parietal cortex and anterior cingulate cortex may be due to differences in patient selection, in the ROI method of semi-quantitative analysis.

In our study all cerebral SPECT studies were performed within a week of performing a battery of PHES test. A significant positive co-relation between PHES and rCBF values in the left superior prefrontal cortex ($r=0.385$, $P=0.006$) was noticed. Superior prefrontal cortex had been linked with functions like attention, working memory, and concentration. Therefore, reduced perfusion in superior prefrontal cortex may be responsible for the deficits in these cognitive domains, which in turn is reflected by the lower scores in the PHES test. Severity of liver disease as determined by CTP score correlated negatively with perfusion in inferior prefrontal cortex ($r=-0.304$, $P=0.003$). Cerebral perfusion in right superior prefrontal cortex correlated negatively with MELD score ($r=-0.323$, $P=0.022$). These findings suggest a greater impairment of rCBF in prefrontal cortex with worsening hepatocyte function.

The semi-quantitative method used for analyzing the rCBF data in this study is based on the calculation of tracer uptake ratios in different cerebral regions with reference to cerebellum and also the whole cortex. In our study statistically significant changes in rCBF values have been obtained in greater number of cortical regions by the region/cortex ratio than the region/cerebellum ratio method. This method is quite laborious, and the results may vary based on the whole brain or cerebellum as denominator for

calculation of ratios. Application of statistical parametric mapping on anatomically standardized templates is a more robust method of analyzing the brain SPECT data and is more specifically suited for cognitive function studies. Although our study suffers from an inherent limitation in the method adopted for rCBF analysis, majority of our findings are in line with the findings of previous studies using SPM.^{30,31} Notwithstanding these shortcomings, this study is an attempt to fill up the gaps in current knowledge regarding pathophysiology and pathogenesis of MHE.

In conclusion, our results suggest that alterations in cognition in cirrhotic patients with MHE may be associated with impaired abnormalities of rCBF.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

1. Amodio P, Montagnese S, Gatta A, et al. Characteristics of minimal hepatic encephalopathy. *Metab Brain Dis* 2004;19:253–67.
2. Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology* 2002;35:716–21.
3. Moore JW, Dunk AA, Crawford JR, et al. Neuropsychological deficits and morphological MRI brain scan abnormalities in apparently healthy non-encephalopathic patients with cirrhosis. *J Hepatol* 1989; 9:319–25.
4. Quero JC, Hartmann IJ, Meulstee J, et al. The diagnosis of sub-clinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. *Hepatology* 1996;24:556–60.
5. Dhiman RK, Saraswat VA, Sharma BK, et al; Indian National Association for Study of the Liver. Minimal hepatic encephalopathy: consensus statement of a working party of the Indian National

- Association for Study of the Liver. *J Gastroenterol Hepatol* 2010; 25:1029–41.
6. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. *Hepatology* 2007;45:549–59.
 7. Romero-Gómez M, Boza F, García-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of over hepatic encephalopathy. *Am J Gastroenterol* 2001;96:2718–23.
 8. Das A, Dhiman RK, Saraswat VA, et al. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. *J Gastroenterol Hepatol* 2001;16:531–5.
 9. Dhiman RK, Kurmi R, Thumburu KK, et al. Diagnosis and prognostic significance of minimal hepatic encephalopathy in patients with cirrhosis of liver. *Dig Dis Sci* 2010;55:2381–90.
 10. Amodio P, Del Piccolo F, Marchetti P, et al. Clinical features and survival of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. *Hepatology* 1999;29:1662–7.
 11. Wein C, Koch H, Popp B, Oehler G, Schauder P. Minimal hepatic encephalopathy impairs fitness to drive. *Hepatology* 2004;39:739–45.
 12. Bajaj JS, Hafeezullah M, Hoffmann RG, Saeian K. Minimal hepatic encephalopathy: a vehicle for accidents and traffic violations. *Am J Gastroenterol* 2007;102:1903–9.
 13. Bajaj JS, Hafeezullah M, Hoffmann RG, et al. Navigation skill impairment: another dimension of the driving difficulties in minimal hepatic encephalopathy. *Hepatology* 2008;47:596–604.
 14. Román E, Córdoba J, Torrens M, et al. Minimal hepatic encephalopathy is associated with falls. *Am J Gastroenterol* 2011;106:476–82.
 15. Sidhu SS, Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). *Am J Gastroenterol* 2011;106:307–16.
 16. Bajaj JS, Heuman DM, Wade JB, et al. Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy. *Gastroenterology* 2011;140:478–87.
 17. Burra P, Senzolo M, Pizzolato G, et al. Does liver-disease aetiology have a role in cerebral blood-flow alterations in liver cirrhosis? *Eur J Gastroenterol Hepatol* 2004;16:885–90.
 18. Iwasa M, Matsumura K, Kaito M, et al. Decrease of regional cerebral blood flow in liver cirrhosis. *Eur J Gastroenterol Hepatol* 2000;12:1001–6.
 19. Iwasa M, Kaito M, Adachi Y, Watanabe Y, Matsumura K, Takeda K. Cerebral blood flow in basal ganglia is correlated with clinical signs of hepatic encephalopathy in patients with liver cirrhosis. *Am J Gastroenterol* 2002;97:763–4.
 20. Iwasa M, Matsumura K, Nakagawa Y, et al. Evaluation of cingulate gyrus blood flow in patients with liver cirrhosis. *Metab Brain Dis* 2005;20:7–17.
 21. Nakagawa Y, Matsumura K, Iwasa M, et al. Single photon emission computed tomography and statistical parametric mapping analysis in cirrhotic patients with and without minimal hepatic encephalopathy. *Ann Nucl Med* 2004;18:123–9.
 22. Tanaka F, Vines D, Tsuchida T, Freedman M, Ichise M. Normal patterns on 99mTc-ECD brain SPECT scans in adults. *J Nucl Med* 2000;41:1456–64.
 23. O'Carroll RE, Hayes PC, Ebmeier KP, et al. Regional cerebral blood flow and cognitive function in patients with chronic liver disease. *Lancet* 1991;337:1250–3.
 24. Atluri DK, Prakash R, Mullen KD. Pathogenesis, diagnosis, and treatment of hepatic encephalopathy. *J Clin Exp Hepatol* 2011; 1:77–86.
 25. Dhiman RK, Saraswat VA, Verma M, Naik SR. Figure connection test: a universal test for assessment of mental state. *J Gastroenterol Hepatol* 1995;10:14–23.
 26. Gupta A, Dhiman RK, Kumari S, et al. Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy. *J Hepatol* 2010;53:849–55.
 27. Weissenborn K, Giewekemeyer K, Heidenreich S, Bokemeyer M, Berding G, Ahl B. Attention, memory, and cognitive function in hepatic encephalopathy. *Metab Brain Dis* 2005;20:359–67.
 28. Catafau AM, Kulisevsky J, Bernal L, et al. Relationship between cerebral perfusion in frontal-limbic-basal ganglia circuits and GIC impairment in patients with subclinical hepatic encephalopathy. *J Nucl Med* 2000;41:405–10.
 29. Yamamoto M, Iwasa M, Matsumura K, et al. Improvement of regional cerebral blood flow after oral intake of branched-chain amino acids in patients with cirrhosis. *World J Gastroenterol* 2005;11: 6792–9.
 30. Iwasa M, Matsumura K, Watanabe Y, et al. Improvement of regional cerebral blood flow after treatment with branched-chain amino acid solutions in patients with cirrhosis. *Eur J Gastroenterol Hepatol* 2003;15:733–7.
 31. Weissenborn K, Bokemeyer M, Ahl B, et al. Functional imaging of the brain in patients with liver cirrhosis. *Metab Brain Dis* 2004;19: 269–80.