Annals of Nuclear Medicine Vol. 18, No. 2, 123–129, 2004

Single photon emission computed tomography and statistical parametric mapping analysis in cirrhotic patients with and without minimal hepatic encephalopathy

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Objective: The early diagnosis and treatment of cognitive impairment in cirrhotic patients is needed to improve the patients' daily living. In this study, alterations of regional cerebral blood flow (rCBF) were evaluated in cirrhotic patients using statistical parametric mapping (SPM). The relationships between rCBF and neuropsychological test, severity of disease and biochemical data were also assessed. ***Methods:*** ^{99m}Tc-ethyl cysteinate dimer single photon emission computed tomography was performed in 20 patients with non-alcoholic liver cirrhosis without overt hepatic encephalopathy (HE) and in 20 age-matched healthy subjects. Neuropsychological tests were performed in 16 patients; of these 7 had minimal HE. Regional CBF images were also analyzed in these groups using SPM. ***Results:*** On SPM analysis, cirrhotic patients showed regions of significant hypoperfusion in the superior and middle frontal gyri, and inferior parietal lobules compared with the control group. These areas included parts of the premotor and parietal associated areas of the cortex. Among the cirrhotic patients, those with minimal HE had regions of significant hypoperfusion in the cingulate gyri bilaterally as compared with those without minimal HE. ***Conclusions:*** Abnormal function in the above regions may account for the relatively selective neuropsychological deficits in the cognitive status of patients with cirrhosis. These findings may be important in the identification and management of cirrhotic patients with minimal HE.

Key words: liver cirrhosis, cerebral blood flow, single photon emission computed tomography, hepatic encephalopathy, cingulate

INTRODUCTION

ENCEPHALOPATHY ASSOCIATED with impairment of consciousness ranging from psychomotor slowing to coma is considered to be indicative of overt hepatic encephalopathy (HE) in cirrhotic patients. On the other hand, some cirrhotic patients with apparently normal mental status, may suffer from abnormalities in cognitive function as detected by sensitive and quantitative neuropsychological examinations and they are therefore considered to have minimal HE. Such cognitive impairment may sometimes be associated with a poor daily living, and thus the early diagnosis and treatment of this condition is important. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have shown alterations in regional cerebral blood flow (rCBF) and cerebral glucose metabolism in cirrhotic patients.[1–6] However, these previous studies reported discrepant results, i.e., reduced rCBF and a focal increase in perfusion or metabolism in the brains of cirrhotic patients.[1–6] We previously reported reduction in absolute rCBF in cirrhotic patients based on quantitative rCBF measurements obtained using SPECT with ^{99m}Tc-ethyl cysteinate dimer (ECD).[7] Although that study showed regional differences in the reduction in rCBF (by 15% in

Received August 4, 2003, revision accepted November 28, 2003.

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Table 1 Clinical characteristics of the patients

Patient		Age (years)	Sex (M/F)	Cause of cirrhosis	Child-Pugh	Plasma ammonia (μg/m*l*) (normal: <30)	Trailmaking A test (sec)	Digit symbol test (points)
1	O.M.	53	M	HCV	C	48		
2	M.K.	63	M	HCV	C	47		
3	K.N.	62	M	Unknown	C	52	110*	28†
4	H.M.	53	M	HCV	B		38	34†
5	F.Y.	54	M	HCV	A	33	59	41
6	F.N.	67	M	HCV	B	50		
7	N.C.	71	M	HCV	A	57	53	37†
8	S.Y.	60	M	HBV	C	28	43	39
9	O.M.	72	F	HCV	B	10	67*	35†
10	N.Y.	58	M	HCV	B		100*	35†
11	M.N.	65	F	HCV	B		65*	22†
12	H.M.	54	M	HCV	C	29	60*	35†
13	H.H.	70	M	HBV	A	37	33	54
14	Y.S.	56	M	HBV	C	104	50	27†
15	I.M.	66	F	HBV	C	27	70*	31†
16	Y.I.	64	M	HCV	B	4	55	26†
17	Y.H.	48	M	HCV	C	66	37	54
18	O.Y.	73	F	HCV	C	34	52	29†
19	B.S.	52	M	HBV, HCV	B	48		48
20	T.Y.	70	M	HCV	B	14	79*	32†

More than 60 sec on the Trailmaking A test (*) and less than 38 points on the digit symbol test (†) were considered to be abnormal values.

the frontal lobe, by 12% in the parietal lobe, and by 10% in the temporal and occipital lobes), the differences were not statistically significant, probably due to the limited accuracy of the manually drawn regions of interest (ROI). In the present study, SPECT images were analyzed using the technique of statistical parametric mapping (SPM) to identify regions of abnormal perfusion in cirrhotic patients with and without minimal HE as evaluated by neuropsychological tests.

MATERIALS AND METHODS

Subjects

Twenty Japanese patients with liver cirrhosis (16 men and 4 women, mean age 62 ± 8 years) were studied. The diagnosis of cirrhosis was based on the results of liver function tests, ultrasonography, computed tomography imaging, laparoscopy and liver biopsy. The cause of liver cirrhosis was viral infection in all patients. No patient with alcoholic liver disease was included in the study. The Child-Pugh severity scores assessed in each patient based on the clinical findings were as follows: 8 patients were in group A, 8 in group B, and 4 patients in group C. The clinical and biochemical characteristics of the patients are summarized in Table 1. None of the patients had overt HE at the time of the examination, and none of them exhibited neuropsychiatric signs or symptoms on standard bedside clinical assessment. Patients with focal brain lesions, severe brain atrophy, abnormalities on computed tomography or magnetic resonance images, or neurological or psychiatric disorders were excluded from the study. None of the patients were receiving any psychoactive drugs.

Control SPECT images were obtained from 20 subjects (16 men and 4 women; mean age, 62 ± 9 years) referred to our neurology department for minor subjective symptoms. These subjects were free of liver disease, neurological disorders or dementia and had normal brain magnetic resonance images. Informed consent was obtained from all subjects, and the study was performed in accordance with the Helsinki Declaration. This investigation was approved by the Ethics Committee of Mie University School of Medicine.

Neuropsychological Tests

All patients had normal scores on minimental status examinations. No patients had dementia. Cognitive function was assessed using a battery of Japanese versions of the Trailmaking A test and a modified digit symbol test revised Wechsler adult intelligence scale, which are widely employed as screening examinations in hepatology clinics in Japan. The Trailmaking A test is used to assess attention and psychomotor speed, and the digit symbol test is used to assess visuospatial capacities. Abnormalities in the results of both neuropsychological tests (values more than 2 standard deviations from the mean values for the age-matched control subjects at our hospital, i.e., more than 60 sec on the Trailmaking A test and less than 38 points on the digit symbol test) were considered to be indicative of minimal HE. Among the 16 cirrhotic patients, 7 showed impairment on both neuropsychological

Table 2 Locations and peaks of significant reductions in relative rCBF

Study	Structure	Coordinates			
		x	*y*	*z*	*Z* score
Liver cirrhosis vs. control (Significance at the $p < 0.01$ level)	Rt. Frontal Lobe, Middle Frontal Gyrus, Gray Matter, Brodmann area 6	36	8	50	4.99
	Rt. Frontal Lobe, Superior Frontal Gyrus, White Matter	18	16	54	3.7
	Rt. Frontal Lobe, Superior Frontal Gyrus, White Matter	16	34	42	3.5
	Rt. Parietal Lobe, Sub-Gyral, White Matter	22	–38	54	3.97
	Rt. Parietal Lobe, Inferior Parietal Lobule, Gray Matter, Brodmann area 40	50	–44	58	3.79
	Lt. Frontal Lobe, Middle Frontal Gyrus, Gray Matter, Brodmann area 8	–22	20	50	3.41
	Rt. Frontal Lobe, Medial Frontal Gyrus, White Matter	8	38	40	3.32
	Lt. Frontal Lobe, Middle Frontal Gyrus, White Matter	–32	38	28	3.28
Liver cirrhosis vs. control ($p < 0.001$)	Rt. Frontal Lobe, Middle Frontal Gyrus, Gray Matter, Brodmann area 6	36	8	50	4.99
	Rt. Frontal Lobe, Superior Frontal Gyrus, White Matter	18	16	54	3.7
	Rt. Frontal Lobe, Superior Frontal Gyrus, White Matter	16	34	42	3.5
	Rt. Parietal Lobe, Sub-Gyral, White Matter	22	–38	54	3.97
Positive neuropsychological tests vs. control ($p < 0.01$)	Rt. Frontal Lobe, Middle Frontal Gyrus, White Matter	34	10	48	4.16
	Rt. Frontal Lobe, Middle Frontal Gyrus, White Matter	44	30	20	3.95
	Lt. Frontal Lobe, Superior Frontal Gyrus, White Matter	–28	12	54	3.76
	Lt. Frontal Lobe, Middle Frontal Gyrus, White Matter	–32	18	46	3.61
	Lt. Frontal Lobe, Superior Frontal Gyrus, White Matter	–30	36	36	3.11
	Rt. Limbic Lobe, Cingulate Gyrus, White Matter	8	28	32	3.31
	Rt. Frontal Lobe, Medial Frontal Gyrus	2	18	48	3.26
	Lt. Frontal Lobe, Medial Frontal Gyrus, White Matter	–8	38	40	2.64
Neuropsychological tests: positive vs. negative ($p < 0.01$)	Inter-Hemispheric	0	12	38	4.08
	Lt. Limbic Lobe, Cingulate Gyrus, Gray Matter, Brodmann area 32	–2	18	46	3.99
	Rt. Limbic Lobe, Cingulate Gyrus	2	24	34	3.96

tests and thus were included in the minimal HE group (Table 1).

Scan Acquisition and Image Processing

Each subject received 555 MBq of ECD by intravenous injection. Ten minutes after the injection of ECD, brain SPECT images were acquired using a three-head gamma-camera system (GCA-9300A/DI, Toshiba, Tokyo, Japan) equipped with low-energy, high-resolution fanbeam collimators. The projection data were obtained using a matrix size of 128 × 128. SPECT images were reconstructed by filtered back-projection using a ramp filter followed by postprocessing with a Butterworth filter. Attenuation correction was performed using Chang's method. The triple-energy window technique was employed for scatter correction.

Image Analysis

To investigative relative changes in rCBF among various conditions voxel by voxel in the whole brain, Image analysis was performed with the statistical parametric mapping software SPM99 (Wellcome Department of Cognitive Neurology, London, UK). The spatial normalization of SPM99 used linear and non-linear transformation and SPECT Template in the SPM99 program. The smoothing of SPM99 used 12 mm full width at half maximum Gaussian filter. The effect of global differences in CBF among SPECT was removed by proportional

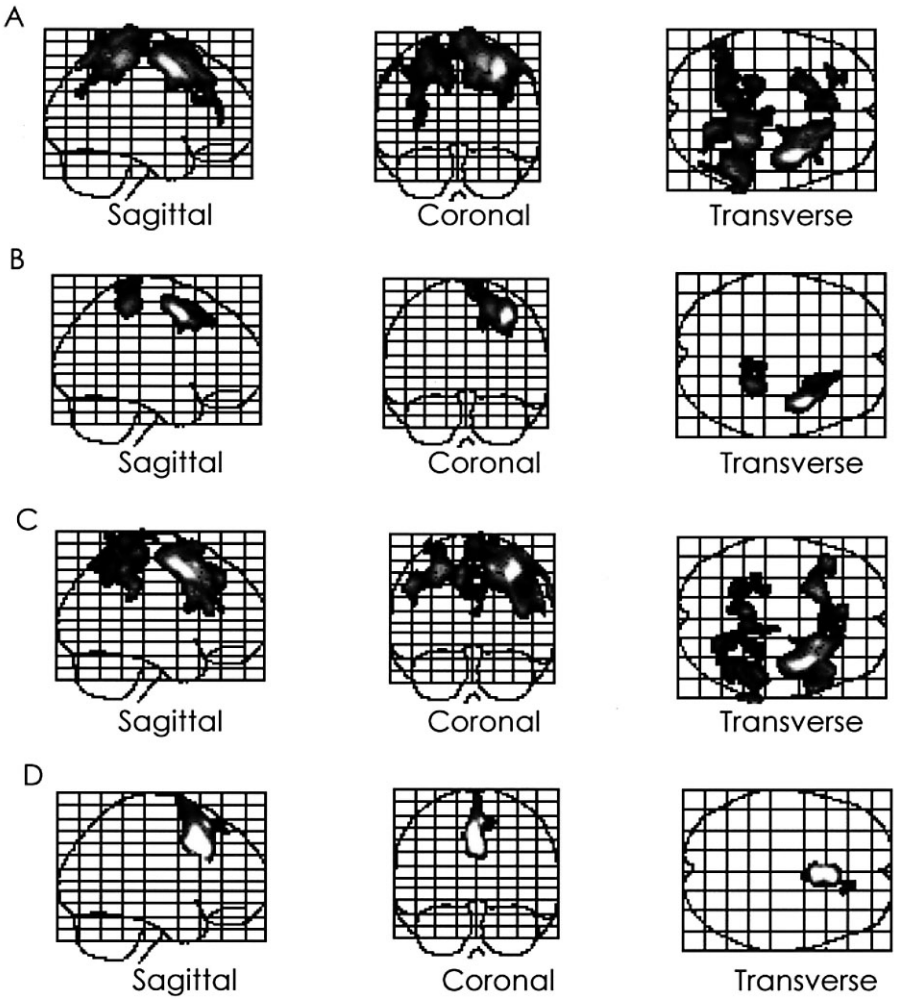

Fig. 1 (A) for liver cirrhosis (n = 20) vs. control (n = 20), $p < 0.01$. (B) for liver cirrhosis (n = 20) vs. control (n = 20), $p < 0.001$. (C) for positive neuropsychological tests (n = 6) vs. control (n = 20), $p < 0.01$. (D) for neuropsychological tests: positive (n = 6) vs. negative (n = 8), $p < 0.01$.

scaling. In the SPM99 program, spatial normalization and smoothing were performed. To evaluate the location of significant clusters, the Montreal Neurological Institute (MNI) coordinates were transformed into Talairach and Tournoux coordinates (Talairach and Tournoux, 1988) and matched to the corresponding volume of interest map by means of the Talairach Daemon soft-ware (Research Imaging Center, University of Texas Health Science Center, San Antonio, TX).[8] The subset of voxels exceeding a threshold of $p < 0.01$ or $p < 0.001$ in omnibus comparison and remaining significant after correction for multiple comparisons (corrected $p < 0.05$) was displayed as a glass brain image by SPM96 for Windows.

RESULTS

Areas of abnormal perfusion that were statistically significant were evaluated in 6 pairs of the groups, and the results are shown in Table 2 and Figure 1.

1. Liver Cirrhosis vs. Controls

In cirrhotic patients (n = 20), SPM showed regions of significant hypoperfusion in the superior and middle frontal gyri, and inferior parietal lobules as compared with the control group (n = 20). These areas included parts of the premotor and parietal associated areas of the cortex (threshold of $p < 0.01$, corrected $p < 0.05$, Fig. 1A). Among the subsets of voxels exceeding a threshold of $p = 0.001$ in omnibus comparison, the areas showing a significant reduction in rCBF in the right hemisphere became more prominent (Fig. 1B).

2. Severity of Liver Dysfunction: Mild vs. Moderate-Severe

The influence of the clinical profile on rCBF was also evaluated. There were no significant differences in cerebral perfusion between the mild (Child-Pugh A, n = 8) and moderate-severe (Child-Pugh B + C, n = 12) liver dysfunction groups.

3. Plasma Ammonia Level: Elevated vs. Normal
There were no significant differences in cerebral perfusion between patients with elevated venous ammonia levels (n = 7) and those with normal levels (n = 7).

4. Patients with minimal HE vs. Controls
In patients with impairment in neuropsychological tests (n = 7), SPM showed significant hypoperfusion in the superior and middle frontal gyri, and cingulate gyri as compared with the control group (n = 20) (Fig. 1C).

5. Patients with minimal HE vs. those without minimal HE
Among cirrhotic patients, those with minimal HE (n = 7) showed regions of significant hypoperfusion in the anterior part of the cingulate gyri bilaterally as compared to patients without minimal HE (n = 9) (Fig. 1D).

6. Patients without minimal HE vs. Controls
There were no significant differences in cerebral perfusion between patients without minimal HE (n = 9) and control subjects (n = 20).

DISCUSSION

HE is a syndrome of cerebral dysfunction associated with liver disease. Patients with cirrhosis may have mild forms of this disorder with no neuropsychiatric signs or symptoms by clinical examination but with abnormalities in quantitative neuropsychological tests. Functional imaging techniques such as rCBF SPECT and fluorodeoxyglucose-PET can show some abnormal findings.[1–6]

An SPM method that not only spatially normalizes PET or SPECT images to a standardized stereotactic space, but can also perform statistical analyses for groups of images has been developed.[9,10] This technique allows automated and operator-independent voxel-based analysis of whole-brain data and it has been increasingly employed for rCBF SPECT in various clinical conditions such as depression, head injury, Parkinson's disease and Alzheimer's disease.[11–14] We applied this technique to ECD SPECT to identify sites of abnormalities in the brains of cirrhotic patients with and without minimal HE by searching for alterations in rCBF in the entire brain.

In the present study, none of the patients had obvious HE by bedside clinical assessment, but some of them had cognitive impairment as revealed by neuropsychological tests. The cognitive function of the patients was assessed using a battery of Japanese versions of the Trailmaking A test and a modified digit symbol test revised Wechsler adult intelligence scale. Patients scoring in the impaired range on both neuropsychological tests were considered to have minimal HE.

In cirrhotic patients with or without minimal HE, SPM analysis using a threshold of p = 0.01 showed significant reductions in rCBF in the superior and middle frontal gyri, and inferior parietal lobules as compared with the control group. In this comparative study, the reduction in rCBF in the right hemisphere was prominent in SPM analysis using a threshold of p = 0.001. In addition, in patients with minimal HE, a significant reduction in rCBF was seen bilaterally in the cingulate gyri as compared to cirrhotic patients without minimal HE. A number of studies have demonstrated that portions of the cortex in the premotor and parietal areas on the right side and the cingulate area bilaterally form a center that mediates attention, analytic capabilities and responsiveness.[15] Defect in attention is an important feature of HE, but attention is not a simple concept; it has been demonstrated that attention depends on an anatomical network that subserves the processes of orientation, higher-level attention, alertness, and so on.[15,16] The anterior cingulate gyri may provide an important connection between widely divergent aspects of attention such as attention to semantic content and visual location.[16] The internal organization of the anterior cingulate gyri shows alternating bands of cells with close connections to the dorsolateral frontal cortex and the posterior parietal lobe.[17] Our data suggest that rCBF is reduced in the associative cortex in the bifrontal and biparietal regions, especially in the right hemisphere, in cirrhotic patients before cognitive dysfunction becomes apparent. However, the reduction in rCBF in the anterior cingulate gyri may become more prominent before cognitive dysfunction develops in cirrhotic patients with minimal HE.

Studies on alterations in rCBF and metabolism have provided discrepant results. O'Carroll et al. reported a reduction in rCBF as measured by SPECT with ^{99m}Tc-hexamethyl-propylene-amino oxime in the right anterior cingulate region in patients with chronic liver disease, including those with alcoholic and non-alcoholic cirrhosis.[5] They also reported an increase in rCBF in the right and left posterior parts of the basal ganglia and the right occipital lobe. Catafau et al. reported that rCBF in the basal ganglia and mesial temporal lobe as measured by ^{99m}Tc-hexamethyl-propylene-amino oxime SPECT is inversely correlated with performance in motor tasks.[2] Lockwood et al. reported an increase in glucose metabolism in the cerebellum, thalamus, and caudate nucleus in PET studies.[3] These findings of hyperperfusion in the basal ganglia were interpreted as the result of prominent and persistent motor sequelae of HE, such as tremor, rigidity, and ataxia. However, in patients of the present study, no area of significant hyperperfusion was identified by ECD SPECT and SPM analysis even using a lower threshold in omnibus comparison. This discrepancy may be due to differences in the uptake characteristics of ECD and hexamethyl-propylene-amino oxime. ECD uptake in the basal ganglia and medial temporal lobe is significantly lower than that of hexamethyl-propylene-amino oxime due to differences in tracer kinetics.[18–21] Interestingly, Trzepacz et al. studied cirrhotic patients with minimal HE using ^{123}I-iodoamphetamine and found a reduction in

rCBF in the right basal ganglia and the frontotemporal regions bilaterally.[6] In addition to the differences in the characteristics of the radiotracers employed, which might have been responsible for the discrepant findings, they placed ROIs manually. We believe that our results are more valid due to the rigor of the SPM analysis. Fluorodeoxyglucose-PET studies showed significant hypometabolism in the cingulate gyrus in patients with nonalcoholic cirrhosis.[4,22] Although fluorodeoxyglucose-PET can detect alterations in regional metabolism, ECD is widespread and easily available in clinical centers with SPECT and is considered to be more useful and practical for the evaluation of cirrhotic patients.

Alterations of rCBF in patients with alcoholic cirrhosis have been reported,[23–25] and were explained as a direct neurotoxic effect of alcohol on the brain in addition to the cerebral sequelae of chronic liver disease. The present study included no patients with alcoholic liver disease, and so the changes in rCBF may be explained by the effect of abnormal levels of metabolites that appear due to liver dysfunction. However, no significant differences in rCBF were observed between patients with severe and mild liver dysfunction, and the reductions in rCBF observed were not likely to be due exclusively to metabolic changes. Although no single metabolic derangement can account for the occurrence of HE, the most frequently cited biochemical factor, among all those that can be related to HE, has been the plasma ammonia level.[26] Lockwood et al. observed regional metabolic abnormalities in cirrhotic patients with hyperammonemia.[22] They also reported increased permeability of the blood-brain barrier to ammonia in patients with cirrhosis and suggested that ammonia might be responsible for the cerebral dysfunction seen in minimal HE.[4] In some of our patients with hyperammonemia, SPM analysis showed no areas of significant abnormal perfusion as compared to the patients without hyperammonemia. This finding does not support the hypothesis of Lockwood et al.

Subtle impairments in cognitive function may be an important cause of occupational and psychosocial morbidity in cirrhotic patients.[27] Dam et al. found that reduction in rCBF improved significantly in almost all areas, reaching control values after liver transplantation.[1] This finding indicates that the diffuse alterations of cerebral perfusion observed in our study are related to liver disease rather than to irreversible anatomic damage. Careful observation is needed in such cases. It has been reported that minimal HE improves along with improvement of the scores in neuropsychological functions following the administration of lactulose.[28] Whether or not rCBF is reversibly improved by such treatment needs to be examined. The findings of the present study may be important in the identification and monitoring of cirrhotic patients with minimal HE.

CONCLUSION

ECD SPECT using an SPM technique as described in this report shows a significant reduction in rCBF in the anterior cingulate gyri in cirrhotic patients with minimal HE as compared with those without minimal HE and normal subjects. We suggest that this regional hypoperfusion may be the pathophysiological basis for the minimal cerebral dysfunction that is often detected by neuropsychological testing in patients with cirrhosis. It is concluded that ECD SPECT with SPM analysis is useful for the objective evaluation of alterations in rCBF in cirrhotic patients.

ACKNOWLEDGMENTS

The authors thank Tokio Kitano, Masakazu Gotoh, and Katsunori Iijima for their technical assistance in the nuclear medicine studies and data analysis.

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