Metabolic Brain Disease, Vol. 10, No. 3, 1995

Evaluation of Neuropsychological Function in Patients with Liver Cirrhosis with Special Reference to Their Driving Ability

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Received 13 March 1995; Revised version received 28 July 1995; Accepted 3 August1995

Ability to drive an automobile was evaluated in 16 patients with well compensated liver cirrhosis. Four tests were performed, namely the emergency reaction test, the continuous emergency reaction test, the signal confirmation test and the accelerator reaction test. Test scores were compared to those of a group of age-matched healthy volunteers. 31% of patients were found to be unfit to drive. Alcoholic cirrhotics fared as poorly as non-alcoholic cirrhotics. In patients with subclinical hepatic encephalopathy (defined by neuropsychologic testing), 44% were unfit to drive. Routine testing of cirrhotic patients for ability to drive could have a major impact on motor vehicle accident rates.

Key words: Liver cirrhosis; driving ability; quantitative psychometric test; performance ability; subclinical hepatic encephalopathy.

INTRODUCTION

By sensitive quantitative neuropsychological tests, abnormalities in performance ability are frequently found in cirrhotic patients without overt mental and neurological symptoms (Zeegen *et al.*, 1970; Rikker *et al.*, 1978). Such patients may show poor attention, lack of concentration, delayed judgment of urgency, and delayed performance. This condition is called subclinical hepatic encephalopathy (Gitlin, 1988). About half of the patients with liver cirrhosis, who are judged not to have clinical hepatic encephalopathy, are believed to fit the category of subclinical encephalopathy. It is highly likely that liver cirrhosis patients with this condition will encounter various accidents, including traffic accidents and accidents in the work place (Gitlin, 1988).

In the present study, driving ability was investigated in cirrhotic patients with or without subclinical encephalopathy by a cathode ray tube (CRT) driving ability test.

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0885-7490/95/0900-0239$07.50/0

PATIENTS and METHODS

Patients

The present study included 16 patients with compensated liver cirrhosis (Table 1). Four patients had a history of excess drinking (more than 80g ethanol / day for longer than 10 years). All alcoholics had been abstinent for 3 years prior to the present study. They consisted of 7 inpatients and 9 outpatients. Most of inpatients were admitted because of having histological diagnosis and checking the presence of hepatocellular carcinoma. The mean age was 59±8 years, and they included 11 men and 5 women. The patients had been diagnosed histologically as having liver cirrhosis. Most of the patients were asymptomatic and working, and they were not on dietary protein restrictions. All of them had driven a car. None of the patients had a history of previous hepatic encephalopathy, nor did they suffer from known neurological or psychiatric disorders. Hepatic myelopathy or hepatic neuropathy was excluded mainly from basic neurological symptoms or signs (Demirci *et al.*, 1992). The intake of drugs influencing the neuropsychological tests was not observed in the control and cirrhotic subjects. At the time of entry into the study, all cirrhotic patients were graded 0 on the encephalopathy scale (Gitlin, 1988), and therefore they showed no neuropsychiatric symptoms.

The diagnosis of subclinical encephalopathy was made by a quantitative psychometric test that included 5 items (Zimmerman *et al.*, 1973; Shiota, 1984; Gitlin *et al.*, 1986; Higuchi *et al.*, 1994), such as reaction time for light (red) and sound, a number connection test (Part A), and digit symbol and block design tests, which are performance subtests in an adult intelligence diagnostic test [Wechsler Adult Intelligence Scale-Revised (WAIS-R)]. These tests are routinely used for clinical assessment of hepatic encephalopathy in our clinic. The detailed methods and control values of psychometric tests were recently reported by us (Higuchi *et al.*, 1994).

All results were assessed according to the normal values of age-matched data collected from 42 control subjects. Abnormalities in two or more items (the values outside mean±2SD for the control subjects) were considered to be indicative of subclinical hepatic encephalopathy. Control subjects for the psychometric test included 24 healthy volunteers and 18 inpatients without liver dysfunction and psychoneurological disorders (intestinal, lung and renal diseases, thyroid and other endocrinological diseases), whose age was 56±11 years. The subjects included 26 men and 16 women.

Nine (56.2%) of 16 patients with liver cirrhosis were diagnosed as having subclinical encephalopathy (Table 1). The cirrhotic patients with and without subclinical encephalopathy were not significantly different from each other with respect to age (encephalopathic group 62.2±5.4 years, and non-encephalopathic group 56.4±8.1 years) or years of scholarity (encephalopathic group 14.2±2.8 years, and non-encephalopathic group 15.1±3.7 years).

Table 1. Summary of clinical and biochemical variables in the cirrhotic patients.

Subject No.	Age(year) /Sex	Etiology	Psychometric test[a]	T.Bil (mg/dl)	Alb (g/dl)	HPT (%)	Child's classification
Inpatients							
1	49 / M	HBV	0	0.9	2.6	74	C
2	58 / M	HCV	0	1.3	2.8	-	C
3	59 / M	HCV	2	0.7	3.3	-	B
4	61 / M	HCV	3	1.2	3.7	>100	A
5	63 / M	HCV	1	0.8	2.8	-	C
6	72 / M	HCV + Alcohol	5	1.7	2.3	87	C
7	54 / F	Alcohol	3	0.9	3.0	71	B
Outpatients							
8	42 / M	HCV	0	1.3	4.4	>100	A
9	58 / F	HCV	4	1.5	3.1	69	B
10	59 / F	HCV	0	0.6	3.5	-	A
11	64 / M	HCV	2	0.8	4.0	-	A
12	67 / F	HCV	3	0.9	3.8	71	A
13	65 / M	Alcohol	4	0.7	4.3	>100	A
14	65 / M	Alcohol	1	0.7	4.6	>100	A
15	59 / M	NBNC	0	0.4	4.7	-	A
16	60 / F	NBNC	2	0.9	4.1	-	A

M : male. F : female. HBV : hepatitis B virus. HCV : Hepatitis C Virus. T.Bil : serum total bilirubin concentration. Alb : serum albumin concentration. HPT : hepaplastin test (a coagulation test).

[a] Number showing abnormal values (the values outside mean ± 2SD for 42 control subjects) on 5 items of a quantitative psychometric test. Abnormalities in 2 or more items were defined as subclinical encephalopathy.

Driving ability test

A CRT driving ability test unit (Takei Kiki Kogyo, Tokyo) [IC Card System Computer Driving Ability Test System <T.K.K. 1128>] was used, and the test followed the National (Japan) Police Agency System Guidelines (The Traffic Division of the Scientific Police Institute, 1989). Eleven standard combinations (for general use, the elderly, the young and others), which include seven test items arranged in suitable alternative ways, are used. For the purpose of the present study, the following four items were selected in order to minimize the physical and mental burden to the subjects.

1) Emergency reaction test. Simple reactions of visual sense and muscle movement (of the feet) were measured. The subjects were instructed to release the right foot from the ersatz accelerator pedal in response to a circular (ca. 10 cm in diameter) red stimulus shown at constant intervals on the center of the CRT monitor. The emergency reaction was tested 5 times within about 15 sec.

2) Continuous emergency reaction test. The degree of prospective and predictive performance was determined. The subjects were instructed to carry out the same action as in the above-described test, but the number of measurements was increased in this test. The test was performed 30 times within about 90 sec.

3) Signal confirmation test. The subjects were instructed to perform quick action in response to stimuli [circular stimulator about 10 cm in diameter in three colors (red, yellow and green)] successively shown at random at constant intervals. Each color was shown 8 times on the center of the CRT monitor. Subjects were told to quickly release the foot from the pedal in response to red, to quickly release the left hand from the button on the left side in response to yellow, and to quickly release the right hand from the button on the right side in response to green. They made a total of 24 responses within about 70 sec.

4) Accelerator reaction test. The subjects were instructed to keep their foot on the accelerator when the green signal was shown, and to quickly release it when the red signal was shown. The test was performed a total of 50 times within about 210 sec.

The mean reaction time (sec) and "maximum-minimum (sec)" of reaction time were adopted as reaction time and variation in reaction time, respectively. The number of erroneous reactions were also counted. Therefore, each item has two or three subitems such as reaction time, variation in reaction time and number of erroneous reactions.

All results were assessed according to the normal values of age-matched data collected from 46 control subjects (healthy volunteers), whose age was 56±8 years. The controls included 29 men and 17 women. The evaluation values of each test obtained in cirrhotic patients were graded '1' through '5' according to the criteria (The Traffic Division of the Scientific Police Institute, 1989); grades '4' and '5' indicate good and excellent ability, grade '3' indicates average ability, and grades '1' and '2' indicate poor and problematic ability respectively.

Overall evaluation values based on all tests examined were evaluated in five grades by checking the number of items of each test showing grade '1' or '2' with the basic type of criteria for the elderly (the most liberal general criteria). According to the overall evaluation, grades "4" and "5" indicate moderately good and good driving ability (safety driver), grade "3" indicates no problem in driving ability, and grades "1" and "2" indicate the need for caution while driving, and the need for guidance and advice.

Biochemical test

Venous blood was obtained from an anticubital vein prior to breakfast in the morning, and blood ammonia levels were immediately determined with an enzymatic kit (Kyowa Medix Co., Tokyo, Japan). The normal value were judged as lower than 80 μg/dl. Other biochemical tests for liver function including hepaplastin test (a coagulation test : Factors II, VII and X involved) similar to prothrombin time (Factors I, II, V, VII and X involved) were routinely determined.

Statistical treatment

The data are expressed as mean±standard deviation (SD). Significant differences between two groups were determined by a non-parametric test, the Mann-Whitney U-test, because it was impossible to evaluate the data from the two groups as a normal distribution. The level of significance was set at less than 5% ($p<0.05$). Significant difference between two factors was tested by 2 x 2 contingency table and 2 x 3 contingency table by Chi-square test for independence, and $p<0.05$ was regarded as significant.

RESULTS

The reaction times on the three reaction tests showed significant prolongation in the liver cirrhosis group as compared to the aged-matched control values (Table 2). The results of the test were not different in alcoholic (4 cases) and non-alcoholic groups (12 cases), and also in inpatient (7 cases) and outpatient groups (9 cases) (data not shown).

Table 2. Reaction time of CRT driving ability test in control subjects and patients with liver cirrhosis

	Emergency reaction test	Continuous emergency reaction test	Signal confirmation test	Accelerator reaction test
		(second)		
Controls	0.330±0.082	0.266±0.058	0.611±0.115	0.484±0.071
Cirrhotic patients	0.332±0.074	0.287±0.038[a]	0.652±0.168[a]	0.535±0.089[b]

[a]$p<0.05$; [b]$p<0.01$; cirrhosis vs. control. No. of control subjects and cirrhotic patients = 46 and 16 respectively.

The frequencies (%) with which the test results were evaluated to be lower than '3' on reaction times (subitem) are shown in Table 3. The frequencies of the evaluation value of lower than '3' on reaction time in the continuous emergency reaction test and signal confirmation test were 68.8% and 37.5% respectively in patients with liver cirrhosis. These values were significantly higher than 26.1 and 8.7% in the control values. However, there were no significant differences in any other subitems such as variation in reaction time or number of erroneous reactions rather than reaction time (data not shown).

The patients with liver cirrhosis were divided into groups with and without subclinical hepatic encephalopathy according to the criteria described under Methods, and the evaluation values determined were similarly compared in two subgroups (Table 3). There was a significant ($p<0.05$) difference in reaction time in the emergency reaction test, patients with subclinical encephalopathy showing slow reaction in this test.

Table 3. Frequencies (%) of the evaluation value of lower than grade '3' on reaction times of the four items of CRT driving ability test in control subjects and cirrhotic patients with and without subclinical encehalopathy

	Emergency reaction test	Continuous emergency reaction test	Signal confirmation test	Accelerator reaction test
Controls (n=46)	10.9% (5)	26.1% (12)	8.7% (4)	26.1% (12)
Cirrhotic patients (n=16)	37.5%[a] (6)	68.8%[b] (11)	37.5% (6)	56.3% (9)
No encephalopathy (n=7)	0.0% (0)	42.9% (3)	14.2% (1)	57.1% (4)
Encephalopathy (n=9)	66.7% (6)	88.9% (8)	55.6% (5)	55.6% (5)

[a]$p<0.05$; [b]$p<0.01$; cirrhosis vs. control; [c]$p<0.05$; encephalopathy vs. no encephalopathy. Number in parentheses indicates number of patients showing the evaluation value of lower than grade '3'.

From the overall evaluation values based on all tests, 31.3% (5 cases) of 16 patients with liver cirrhosis were considered to have poor driving ability ("1" + "2") (Table 4). This value was significantly higher than 4.3% in the control results. A significant difference of CRT driving ability test between control subjects and cirrhotic patients was observed (2 x 3 contingency table by Chi-square test : $p<0.05$). Concerning the cirrhotic patients with subclinical encephalopathy, 44.4% (4 cases) of the 9 patients showed significantly poor driving ability ("1" + "2"). A significant difference of the test between the presence and absence of subclinical encephalopathy in cirrhotic patients was also observed (2 x 3 contingency table by Chi-square test : $p<0.01$).

Correlation between reaction times of CRT driving ability test and quantitative neuropsychological test was evaluated in cirrhotic patients with and without subclinical encephalopathy, and a low reciprocal correlation ($r = -0.515$) between the overall evaluation values for CRT driving ability test ("1" through "5") and time (sec) for number connection test (normal value : < 63 seconds). Furthermore, there was a high reciprocal correlation ($r = -0.708$) between the overall evaluation value of driving ability test ("1" through "5") and blood ammonia concentration (normal value : < 80 μg/dl) (figure 1). However, no other data of routine liver function tests were correlated with CRT driving ability test.

Table 4. The overall evaluation value of CRT driving ability test in control subjects and cirrhotic patients with and without subclinical encephalopathy

	Overall evaluation value		
	"4" + "5"	"3"	"1" + "2"
Controls[a] (n=46)	56.5% (26)	39.1% (18)	4.3% (2)
Cirrhotic patients[a] (n=16)	43.8% (7)	25.0% (4)	31.3% (5)[c]
No encephalopathy[b] (n=7)	58.7% (6)	0.0% (0)	14.3% (1)
Encephalopathy[b] (n=9)	11.2% (1)	44.4% (4)	44.4% (4)

[a]$p<0.05$; cirrhosis vs. control, [b]$p<0.01$; encephalopathy vs. no encephalopathy: Difference based on 2 x 3 contingency table by Chi-square test; [c]$p<0.005$; cirrhosis vs. control: Difference based on 2 x 2 contingency table by Chi-square test. Number in parentheses indicates number of patients showing the overall evaluation value indicated.

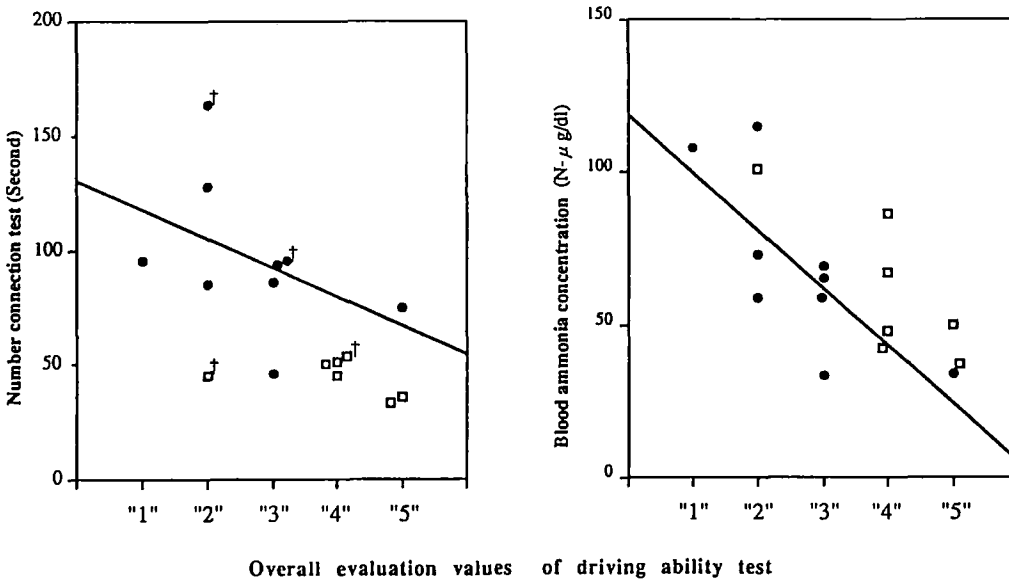

Figure 1. Correlation between number connection test (Part A) and blood ammonia concentration and overall evaluation value of driving ability test in cirrhotic patients with (●) and without (□) subclinical encephalopathy ($y = 130.2 - 12.7x$ and $y = 119.0 - 19.0x$). Number connection test (Trailmaking test Part A. Normal < 63 seconds) can be performed within 53 seconds in 42 control subjects. Venous blood ammonia concentrations (normal : < 80 μg/dl) were determined by an enzymatic kit. † : Hyperammonemia (80 μg/dl or above).

DISCUSSION

The results of Schomerus and colleagues (Schomerus *et al.*, 1981) indicate that 60-70% of Western patients with liver cirrhosis show impaired driving, suggesting that it is important to consider precautions from a medical approach. However, their data were based on an indirect evaluation of driving ability using four types of quantitative neuropsychological tests. An analysis which makes use of a dedicated, up-to-date instrument to evaluate driving ability, is reported here for the first time. Concrete examples of traffic accidents due to hepatic encephalopathy have already been reported by us (Watanabe, 1992); the overall evaluation value for the driving ability test was "1", although there was a time lag between the accident and the test. It has also been observed that a score of "1" improved to "3" in patients in whom the blood ammonia concentration was stabilized by the treatment of hepatic encephalopathy.

The CRT driving ability test is performed to guide safe driving by the evaluation method whereby values for the subitems are converted to evaluation values (grade '1' to '5') rather than actual reaction time (sec) (The Traffic Division of the Scientific Police Institute, 1989). Although the test should be carried out by trying outside-driving, CRT test is well validated. A good correlation was observed between the quantitative neuropsychological test and CRT driving ability test, suggesting that both these tests have similar significance. The CRT driving ability test enables more multilateral analysis and can reflect more daily activities than the other tests. Therefore, this test can be used to identify cirrhotic patients with subclinical encephalopathy. However, since the test uses a specific instrument, it may not be easy to perform at the bedside or on an ambulatory basis.

In the present study, cirrhotic patients with hepatic myelopathy or hepatic neuropathy, who might show abnormality of the reaction time depending upon the function of spinal cord or peripheral nerve, were excluded by clinical evaluation. However, uncommon complication of subclinical myelopathy or neuropathy can not be excluded from the patients in the present study, and thus nerve conduction study should be included in future investigations.

The underlying mechanism(s) responsible for the impaired driving ability test reflecting subclinical encephalopathy remain(s) to be determined. A previous study (Tarter *et al.*, 1984) indicates that they reflect hepatocellular function *per se* or the sequel of portal-systemic shunting through collaterals. In the present study, no significant difference was found between the severity of liver disease and the extent of driving ability test impairment. Blood ammonia levels were negatively correlated with the overall evaluation of the driving ability test. Ammonia can induce the metabolic impairment of neurotransmitter amino acids and energy production in the brain, morphological changes of astrocytes, and dysfunction of synaptosomal membranes, and thus interfere with the normal electrophysiological properties of the brain (Cooper *et al.*, 1987).

Previous reports (Moore *et al.*, 1989) found a poor correlation between measurements of magnetic resonance image (MRI) and neuropsychological performance suggesting that these abnormalities have a metabolic rather than a morphologic basis, and this view is supported by the fact that they are improved by oral lactulose or low-protein diet.

The fact that the neuropsychiatric deficits in alcoholic and non-alcoholic cirrhotics are similar may suggest that the observed changes are due to hepatic encephalopathy itself and not to the effect of alcohol or nutritional deficiency on the central nervous system (Gitlin *et al.*, 1986). This is supported by the fact that these changes improve significantly upon instituting treatment for portal-systemic encephalopathy.

Particular care should be paid to daily activities in the high-risk portal-systemic encephalopathy group patients, those with high blood ammonia and those with a history of hepatic encephalopathy, etc. Appropriate guidance is required. Some patients may be at risk without it being noticed by their family, co-workers, or friends. Nothing unusual may be noticed until an accident occurs. Therefore, in seeing high-risk patients, routine periodic quantitative neuro-psychological evaluations of all patients with cirrhosis is advocated in order to detect subclinical hepatic encephalopathy and to prevent its possible deterioration into clinical encephalopathy and to decrease the risk of an automobile or work place accident.

Further studies are clearly required on a larger population of clinically asymptomatic patients with chronic liver disease as well as in patients with subclinical and overt encephalopathy in order to identify tests that discriminate driving impairments in these patients.

ACKNOWLEDGEMENT

This work was supported in part by grants from the Scientific Research Fund of the Ministry of Education (No. 01570397, 02454231 and 05454244). We wish to thank Dr. Tetsuya Shiota for his continuous guidance and support throughout this investigation.

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