Driving Performance Among Patients with Cirrhosis Who Drove to Their Outpatient Hepatology Clinic Appointments

Paul J. Thuluvath^a, Anantha Nuthalapati^b, Jennifer Price^c, Anurag Maheshwari^a

^aUniversity of Maryland School of Medicine & Mercy Medical Center, Medicine, 301 Saint Paul Place, Baltimore, MD 21202, United States,

^bMercy Medical Center, Baltimore, MD 21202, United States and ^cDepartment of Medicine, University of San Francisco School of Medicine, San Francisco, CA, United States

Background: Minimal hepatic encephalopathy (MHE) may adversely affect driving skills. **Aims:** To compare the driving performance of cirrhotic patients with and without prior HE as well as controls using a driving stimulator and to correlate psychometric testing with driving performance. **Methods:** Adult patients with cirrhosis, who drove to the outpatient clinic for their routine appointments underwent a battery of driving and psychometric tests including number connection tests A & B (NCT-A and NCT-B), digit symbol test (DST) and critical flicker and fusion frequency (CFF) testing. **Results:** Cirrhotics had significantly higher NCT-A (39.3 s vs. 31.2 s, $P = 0.006$) and DST scores (317 s vs. 245 s, $P = 0.012$), and lower CFF scores Fusion (33 vs. 36 Hz, $P = 0.05$), Flicker (35 vs. 42 Hz, $P = 0.007$) than controls. There was no difference in NCT-A, DST and CFF scores between patients with and without HE. Ten (22%) patients, 7 (27%) with prior HE and 3 (15%) without prior HE, had abnormal NCT-A scores (i.e. $>$ control mean $\pm$ 2SD), and 12% of patients with prior HE had one or more driving test accidents, while controls and patients without prior HE had none. Patients with cirrhosis were more likely to hit pedestrians compared to controls ($P = 0.05$). There was no correlation between CFF, DST and NCTB scores with driving performance test results. **Conclusions:** Unlike previous reports, no significant differences were noted between the patients with and without prior HE on psychometric testing, and on the driving simulator, but driving accidents were seen in only those with previous history of HE. (J CLIN EXP HEPATOL 2016;6:3–9)

Previous studies have shown that minimal hepatic encephalopathy (MHE) may adversely affect driving skills. MHE, a neurocognitive complication of cirrhosis characterized by impairments of attention, response inhibition, visual-motor coordination, and psychomotor speed in the absence clinical evidence of hepatic encephalopathy, is very common in patients with cirrhosis.^{1–4} It has been suggested that the presence of MHE may predict future development of overt HE and may also impair daily functioning and health-related quality of life.^{5–9} In another study, cognitive impairment (learning capacity and working memory) was found to be significantly impaired in patients with history of overt HE despite adequate therapy when compared to patients without prior overt HE. Moreover, there was cumulative worsening of cognitive function

with recurrent episodes of overt HE.¹⁰ Motor vehicle accidents are among the leading causes of morbidity and mortality in the United States, and it has been shown that patients with MHE have higher rates of traffic violations and motor vehicle accidents.^{11–15} In one study, Schomerus et al. examined driving fitness in 40 patients with cirrhosis and found that 60% of patients may be unfit to drive on the basis of psychometric testing.¹⁶ In another study, Wein et al. used a standardized 90-min on-road driving test and found that the fitness to drive a car was impaired in cirrhotic patients with MHE.¹⁷ In contrast, a third study reported that patients with cirrhosis and porto-systemic shunting did not exhibit a major impairment in their performance either on a driving simulator or during actual driving conditions when compared to matched controls.¹⁸

Despite some contrasting studies, there is increasing evidence to suggest that patients with MHE may have impaired driving skills resulting in higher automobile accidents when compared to those without MHE.^{19,20} A decline in cognitive function including impaired visual orientation, attention span, reactivity, stress tolerance and speed of mental processing could perhaps explain the higher incidence of automobile accidents.^{21,22} Anecdotally, the authors have seen many patients with significant cognitive impairment due to encephalopathy drive alone to their appointments at a hospital based in

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Address for correspondence: Paul J. Thuluvath, University of Maryland School of Medicine & Mercy Medical Center, Medicine, 301 Saint Paul Place, Baltimore, MD 21202, United States.

E-mail: thuluvath@gmail.com

Abbreviations: CFF: critical flicker and fusion frequency; DST: digit symbol test; HE: hepatic encephalopathy; MHE: minimal hepatic encephalopathy (MHE); NCT-A: number connection tests A; NCT-B: number connection tests B

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Baltimore city. There are no current recommendations regarding routine assessment of driving abilities of patients with liver disease, nor is there consensus on the optimal testing modality to determine such patients' fitness to drive. Moreover, motor vehicle authorities provide no guidelines for driving tests or license renewal in patients with cirrhosis. In this study, our aims were to compare the driving performance of cirrhotic patients with and without prior HE as well as healthy controls using a driving simulator task and to determine whether abnormal psychometric testing was associated with impaired driving performance.

METHODS

Adult outpatients (age >18 years) with cirrhosis who drove to the outpatient hepatology clinic for their routine appointments were asked to participate in the study. Patients were not informed about the study prior to their visits. Patients were excluded if they had untreated overt HE, or other neurological diseases that could potentially cause impaired cognition or impaired motor skills (e.g. Parkinson's disease). Patients with cirrhosis were excluded if they had consumed alcohol within 6 months. Healthy controls, who accompanied the patients, were excluded if they had consumed alcohol (socially) within 48 h before testing. Patients and controls were excluded if they were on benzodiazepines, antipsychotics and antiepileptic medications.

After obtaining written informed consent, all subjects answered a detailed sleep history questionnaire (sleeping time <6 h/night, sleep latency >30 min, awakenings (more than 3 episodes/night), daytime sleepiness (more than 4 episodes/week), daytime naps (more than 50 min/day), and then underwent a battery of psychometric testing including number connection tests A & B (NCT-A and NCT-B), digit symbol test (DST) and critical flicker and fusion frequency (CFF) testing. The control cohort consisted of family members of patients who accompanied the patients to their clinic visit. This study was conducted over a period of 6 months, and the study was approved by Institutional Review Board of the Mercy Medical Center and the Johns Hopkins Hospital.

NCT-A is a test of visuo-spatial orientation and psychomotor speed, and in addition to visuo-spatial orientation and psychomotor speed, NCT-B gauges the ability to shift attention. DST examines visuo-constructive abilities.²³ CFF is a computerized psychometric test that evaluates the maximum frequency, at which a flickering light source can still be perceived to flicker and measures a threshold for the fusion of these lights.²⁴ CFF threshold measures visual discrimination and general arousal, and has shown modest dependence on age and educational background.^{25,26} For the purpose of this study, we considered control mean $\pm$ 2SD as abnormal for NCT-A (>46.3 s), NCT-B (>193.1 s), DST (>367), fusion (44.6) and flicker (55.5) testing.

The driving simulator task was performed on the same session immediately after the psychometric testing. The Beta Research Model 1100 driving simulator with STISim Drive simulation software (originally developed for the U.S. Department of Transportation) was used in this study. Details about the simulator set-up and software can be found in a prior publication of driving abilities in cirrhotic patients.¹⁹ After a brief training to get acquainted with the simulator, all participants underwent the driving simulation task. The driving simulator test is comprised of two sections each lasting approximately 20 min each. The first section is called the driving and divided attention task and simulates driving in various terrains with differing road conditions and speed limits (e.g. city traffic, suburban roads, hilly terrain and highway speeds) while assessing the number of accidents and traffic violations. The second section is a navigational task in which patients are asked to travel from point A to B and back using a map. The road signs along the route are oriented to provide considerable assistance in following the designated route. Failure to follow the road signs and the designated route is assessed by the number of illegal turns that are recorded as errors during the task.

Wilcoxon rank sum test was used for statistical analysis of continuous variables and chi-square test for binary variables. The limit for statistical significance was set at $P \leq 0.05$. Stata 11.2 (StataCorp) was used for the analysis.

RESULTS

Forty-six patients with cirrhosis, 20 without and 26 with previous history of HE were compared to 17 healthy controls. The demographics of all groups are listed in Table 1. Compared to the cirrhotic group, controls were younger (mean age 44 years vs. 56.7 years, $P < 0.001$) and therefore had less driving experience (mean 22.7 years vs. 36.5 years, $P < 0.001$) were significantly lower in control group Chronic hepatitis C (50%) was the most common etiology of liver disease. The proportion of patients with alcoholic liver disease was similar among the two groups of patients with cirrhosis. Only two patients with cirrhosis had any alcohol within 6 months, and these two patients had non-alcoholic liver disease and had only an occasional drink within 6 months. None of the healthy controls had alcohol within 48 h before testing. None of our patients or controls was on benzodiazepines, antipsychotics, and antiepileptic medications. Patients with a history of HE had more severe liver disease than patients without prior HE as measured by MELD and CPT scores (Table 1). Complaints about sleep disturbance were significantly higher in individuals with prior HE (62%) compared to patients without prior HE (25%) and control group (6%). Educational background and driving citations in the last 3 years prior to the study were similar among all three groups. Among those with a prior driving citation, the majority of patients and controls had only 1 citation; one

Table 1 Demographics of patients and controls.

	Group A Controls (n = 17)	Group B No h/o HE (n = 20)	Group C h/o HE (n = 26)	P value
Age in years (mean)	44	57	56	<0.001
Male (%)	6 (35%)	7 (35%)	12 (46%)	NS
Education				NS
Up to 8th grade		2 (10%)	2 (7.7%)	
High school	7 (41%)	12 (60%)	12 (50%)	
Bachelors	7 (41%)	4 (20%)	7 (27%)	
Masters	3 (18%)	2 (10%)	4 (15%)	
Driving experience (yrs)	22.7	37.4	35.8	<0.001 (A vs. B + C)
Driving citations in last 3 yrs	2 (13%)	3 (15%)	3 (12%)	NS
Etiology of liver disease				
No liver disease	15 (88%)			
Alcohol		4 (20%)	6 (23%)	
HCV	2 (12%)	10 (50%)	13 (50%)	
HBV		2 (10%)		
AIH, PBC or PSC		2 (10%)	4 (15%)	
Cryptogenic/NASH		2 (10%)	1 (3.9%)	
Other			2 (7.7%)	
Medication use for HE			19 (73%)	
Sleep disturbance complaints	1 (6%)	5 (25%)	16 (62%)	0.005 (A vs. B + C); 0.01 (B vs. C)
MELD (mean)		9.2	11.6	0.04 (B vs. C)
CPT (mean)		6.2	7.8	<0.001 (B vs. C)

control had 2 citations and one patient had 3 citations. The majority (73%) of patients with previous history of HE were on lactulose, and three were on combination therapy.

The cirrhotic cohort had significantly higher NCT-A (39.3 s vs. 31.2 s, $P = 0.006$) and DST scores (317 s vs. 245 s, $P = 0.012$) than controls. Please note that we have provided the time taken to complete the entire task for DST instead of the standard 90s test. The CFF scores were significantly lower in cirrhotics than controls (Fusion 33 vs. 36 Hz, $P = 0.05$, Flicker 35 vs. 42 Hz, $P = 0.007$) (Table 2). Among subjects with and without prior HE, NCT-A (38.1 s vs. 40.2 s, $P = 0.32$), DST (305 vs. 327, $P = 0.33$), fusion

(31.8 vs. 33.6, $P = 0.7$) and flicker (34.9 vs. 35.1, $P = 0.4$) scores were similar. When data were analyzed using previously reported Flicker cut-off of 39 (30% with no HE, 8% with HE) or 38 (35% with no HE and 8% with HE), there were no differences between those with and without history of HE. Ten (22%) patients, 7 (27%) with prior HE and 3 (15%) without prior HE, had abnormal NCT-A scores (i.e. >control mean $\pm$ 2SD) (Table 2).

Driving test performance results are shown in Table 3. Twelve percent of patients with prior HE had one or more driving test accidents, while controls and patients without prior HE had none. Patients with cirrhosis were more likely to hit pedestrians on the driving simulator compared to

Table 2 Neuropsychometric and CFF test results.

	Group A Controls (n = 17)	Group B No h/o HE (n = 20)	Group C h/o HE (n = 26)	P value
NCTA mean (SD), median (IQR)	31.2 (7.55), 30 (25,37)	38.1 (11.88), 37 (28,44)	40.2 (10.51), 40 (32,48)	0.006 (A vs. B + C)
DST: mean (SD), median (IQR)	245 (61), 228 (203,273)	305 (119), 250 (212,380)	327 (110), 306 (262,381)	0.01 (A vs. B + C)
Fusion mean (SD), median (IQR)	35.7 (4.3), 35.8 (32.5,38)	31.8 (8.02), 33.2 (31.4,35.9)	33.6 (1.61), 33.6 (32.6,34.8)	0.05 (A vs. B + C)
Flicker mean (SD), median (IQR)	41.7 (6.89), 39.3 (36.5,47)	34.9 (9.72), 35.4 (32.9,39.3)	35.1 (2.58), 35.6 (33.1,37)	0.007 (A vs. B + C)

Table 3 Driving test results.

Driving test variables	Group A Controls (n = 17)	Group B No h/o HE (n = 20)	Group C h/o HE (n = 26)	P value			
Attention test incorrect responses							
0	2 (13%)	1 (5%)	3 (12%)	NS			
>1	14 (88%)	19 (95%)	23 (88%)				
Driving test accidents							
0	16 (100%)	20 (100%)	23 (88%)	NS			
>1			3 (12%)				
Collisions							
0	9 (56%)	16 (80%)	21 (80%)	NS			
>1	7 (44%)	4 (20%)	5 (19%)				
Pedestrians hit							
0	5 (31%)	8 (40%)	5 (19%)	0.05 (A vs. B + C)			
>1	11 (69%)	12 (60%)	21 (81%)	NS (B vs. C)			
Navigational task accidents							
0	7 (44%)	7 (35%)	9 (38%)	NS			
1–3	8 (50%)	9 (45%)	11 (46%)				
>4	1 (6.3%)	4 (20%)	4 (17%)				
(A) Driving test results based on the Spanish thresholds for CFF							
Driving test variables	Normal CFF (<38)			Abnormal CFF (>38)			P value
	Controls (n = 9*)	No h/o HE (n = 13)	h/o HE (n = 24)	Controls (n = 7)	No h/o HE (n = 7)	h/o HE (n = 2)	
Attention test incorrect responses >1	8/9 (89%)	12/13 (92%)	21/24 (88%)	6/7 (86%)	7/7 (100%)	2/2 (100%)	NS
Driving test accidents >1	0/9	0/13	2/24 (8%)	0/7	0/7	1/2 (50%)	NS, in HE group, 0.08
Collisions >1	4/9 (44%)	3/13 (23%)	4/24 (16%)	3/7 (43%)	1/7 (14%)	1/2 (50%)	NS
Pedestrians hit >1	7/9 (78%)	8/13 (62%)	20/24 (83%)	4/7 (57%)	4/7 (57%)	1/2 (50%)	NS
Navigational task accidents >1	5/9 (56%)	9/13 (69%)	14/24 (58%)	4/7 (57%)	4/7 (57%)	1/2 (50%)	NS
(B) Driving test results based on the German thresholds for CFF							
Driving test variables	Normal CFF (<39)			Abnormal CFF (>39)			P value
	Controls (n = 9*)	No h/o HE (n = 14)	h/o HE (n = 24)	Controls (n = 7)	No h/o HE (n = 6)	h/o HE (n = 2)	
Attention test incorrect responses >1	8/9 (89%)	13/14 (93%)	21/24 (88%)	6/7 (86%)	6/6 (100%)	2/2 (100%)	NS
Driving test accidents >1	0/9	0/14	2/24 (8%)	0/7	0/6	1/2 (50%)	NS, in HE group, 0.08
Collisions >1	4/9 (44%)	3/14 (21%)	4/24 (16%)	3/7 (43%)	1/6 (17%)	1/2 (50%)	NS
Pedestrians hit >1	7/9 (78%)	8/14 (57%)	20/24 (83%)	4/7 (57%)	4/6 (67%)	1/2 (50%)	NS
Navigational task accidents >1	5/9 (56%)	9/14 (64%)	14/24 (58%)	4/7 (57%)	4/6 (67%)	1/2 (50%)	NS

*1 control with normal CFF (<38) didn't take the driving test.

controls ($P = 0.05$). Attention test incorrect responses, collisions, and navigational task accidents were similar in three groups. All patients with abnormal NCT-A scores failed the pedestrian portion of the driving test compared to 64% of patients with normal NCT-A scores ($P = 0.025$). There was no correlation between CFF, DST and NCTB scores with driving performance test results.

Subgroup analysis of neuropsychometric and driving simulator test results of two groups of patients with history of HE (on and off lactulose) are shown in Table 4. Abnormal NCT-A scores were seen in 32% of patients who were on lactulose cohort compared to 29% who were not on lactulose ($P = 1.0$). Though the mean NCT-A and DST scores were higher in the subgroup receiving lactulose,

Table 4 Sub-Group Analysis of patients with history of HE (patients on Lactulose and patients not on lactulose – Neuropsychometric and Driving test results.

Tests	Patients on Lactulose (n = 19)	Pts not on Lactulose (n = 7)	P value
NCT-A (mean ± SD)	44.5 (13.0)	36.7 (13.0)	NS
DST (mean ± SD)	340.6 (115.2)	290.9 (96.8)	NS
Fusion (mean ± SD)	33.6 (1.9)	34.2 (1.8)	NS
Flicker (mean ± SD)	35.0 (3.0)	35.0 (1.7)	NS
Pedestrian hit	15/19 (79%)	6/7 (86%)	NS
Navigational task accidents	11/19 (58%)	4/7 (57%)	NS
Collisions	5/19 (26%)	2/7 (28.5%)	NS

surprisingly there were no significant differences in test results among the two cohorts.

DISCUSSION

This study showed that despite having a higher severity of liver disease and higher prevalence of sleep disturbance, cirrhotic patients with a prior history of HE performed similar to cirrhotic patients without HE on psychomotor testing and on the driving simulator. Despite having significantly abnormal values on psychometric testing compared to controls, patients with cirrhosis performed similarly to controls on the driving simulator, with the exception of the pedestrian portion. Patients with abnormal NCT-A scores were more likely (100%) to fail the pedestrian portion of the driving test compared to those with normal NCT-A (64%) scores.

To our surprise, no significant differences were noted between the patients with and without prior HE on psychometric testing, and on the driving simulator, although driving accidents that were seen in only those with previous history of HE. This is in contrast to previous studies that have shown that patients with MHE had significantly worse performances in car handling as rated by professional driving instructors and performed poorly on total judgment and other driving categories (adaptation to driving situation, cautiousness, and handling the car).¹⁷ Driving instructors also had to intervene at a significantly higher rate in MHE patients to prevent a traffic accident during on-road driving evaluation. In our study, however, 73% of patients with previous history of HE were on lactulose, and this could have resulted in significant improvements in psychometric functions and driving simulator performance.^{27–29} A recent cost effectiveness analysis using a Markov model suggested that lactulose treatment prevented motor vehicle accidents in patients with cirrhosis irrespective of whether they were on lactulose or not.²⁹ Subgroup analysis of patients with previous history of HE in our study showed similar performances in neuropsychometric and driving simulator tests regardless of lactulose use. Unlike several previous studies, we did not

exclude patients who were on lactulose as we were interested to assess the driving skills of patients with cirrhosis who drove to the outpatient clinic appointment without any prior knowledge of the study. In that respect, our study was very close to the real world experience. In addition, because our study was limited to patients who drove to the appointment, patients with more advanced liver disease or overt HE were less likely to be included. The intermittent nature of HE and relatively small sample size could also explain the similarity of test results among patients with and without previous HE. Nevertheless, it is important to note that only those with previous HE had driving accidents on the simulator.

We could not determine the independent effect of etiology of liver disease on driving skills because of the small sample size. Previous alcohol use was similar in both groups with cirrhosis, and none of our patients had alcohol for at least 48 h before the tests. Additionally, we have previously observed that after adjusting for the severity of liver disease, the severity of cognitive impairment is similar among alcoholic and non-alcoholic cirrhotic patients.³⁰ Therefore, we do not believe that a large sample would show any differences between alcoholic and non-alcoholic liver disease. Other factors that affect driving performance, i.e. age, driving experience, and driving citations (in the last 3 years) were not significantly different in groups B and C. Educational background is another confounder that can influence neuropsychological performance but was similar across all three groups.^{31,32} Although it could be argued that driving on the road is very different compared to a simulator, the simulator kept the environmental factors that result in traffic accidents as constant allowing us to study human factors in greater detail.³³ One limitation of our study was the use of a driving simulator without a vestibular input, since it has been shown that vestibular input could also guide navigation and driving.³⁴

The number connection test (NCT) is the most widely used test in the psychometric assessment of cirrhotic patients. NCT-A evaluates the time needed to connect the randomly spread circles from 1 to 25 on a single sheet of paper. The NCT-A is a test of visuo-spatial orientation

and psychomotor speed and these processes are required for safe driving practices. NCT is capable of detecting mild mental dysfunction in cirrhotic patients. The impairment in attention and speed of mental processing adversely affects an individual's ability to react in unexpected traffic conditions. In this study all patients with abnormal NCT-A, regardless of prior history of HE, failed the pedestrian portion of the driving test owing to prolonged reaction times in applying brakes. Although NCT-A could be used as a tool to screen cirrhotic patients at risk for driving errors, it is important to note that those with normal NCT-A also failed the pedestrian portion of the driving test suggesting that we need better assessment tools to test driving skills.

Critical flicker frequency (CFF) is a simple method that tests the ability of a patient to perceive flickering and its fusion threshold. A previous study had shown that cirrhotics with abnormal CFF test results were at risk of developing overt HE in the first year of follow-up.³⁵ These results have not been replicated in the US population.^{36,37} In our study, although CFF test results were significantly abnormal in the cirrhotic cohort, there was no correlation between CFF test results and performance on driving simulator. This observation may suggest that CFF may not be a good screening test to evaluate driving skills.

In our study, we could not identify a single or a combinations of tests that could be used as a screening tool except that those with previous HE were more likely to have driving accidents and those with abnormal NCT-A were more likely to fail the pedestrian portion of the driving test. Even if we were to find a combination of tests, reporting a patient as medically unfit to drive may have a serious impact on patient's quality of life and on the physician-patient relationship. A Canadian survey clearly demonstrated that physicians believe that reporting their patient as unfit to drive would negatively affect their relationships.³⁸ It appears that the attitude of medical community toward this complex subject varies in different countries partly because of the knowledge gap, differences in local driving regulations and also its interpretation.³⁹ Although road traffic accidents are more common among patients with cirrhosis, we need to develop stringent guidelines and more refined tools to evaluate the driving habits of cirrhotic patients prior to reporting driving infarctions to the motor vehicles department.

CONFLICTS OF INTEREST

The authors have none to declare.

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