Minimal Hepatic Encephalopathy Impairs Fitness to Drive

Christian Wein,[1] Horst Koch,[2] Birthe Popp,[1] Gerd Oehler,[2] and Peter Schauder[3]

It has been suggested that the ability to drive a car is impaired in patients with cirrhosis of the liver and minimal hepatic encephalopathy (MHE). However, the only study using an on-road driving test did not reveal such an impairment. In a prospective controlled study, we evaluated patients with cirrhosis of the liver for MHE and the ability to drive a car. MHE was diagnosed using three psychometric tests: Number Connection Test Part A, Digit Symbol Test, and a Complex Choice Reaction Test. In a standardized on-road driving test (22 miles, 90 minutes), designed for patients with brain impairment, a professional driving instructor blind to the subjects' diagnosis and test results assessed the driving performance. Four global driving categories (car handling, adaptation to traffic situation, cautiousness, maneuvering), 17 specific driving actions (*e.g.*, changing lanes, overtaking, etc.), and a total score of driving performance were rated using a 6-point scale. Of 274 consecutive patients with liver cirrhosis, 48 fulfilled the medical and driving inclusion criteria, 14 of them with and 34 without MHE. Forty-nine subjects in a stable phase of chronic gastroenterological diseases and with normal liver findings served as controls. The total driving score of patients with MHE was significantly reduced in comparison to either cirrhotic patients without MHE or to controls ($P < .05$). Significant differences in ratings were found in the following driving categories: car handling, adaptation, and cautiousness. Significant differences were also found in specific driving actions. The instructor had to intervene in the driving of 5 of the 14 MHE patients to avoid an accident, significantly more than in cirrhotic patients without MHE and in controls. There was no significant difference in any driving category or specific driving action in cirrhotic patients without MHE compared to controls. In conclusion, fitness to drive a car can be impaired in patients with MHE. Therefore, patients with liver cirrhosis should be tested for MHE and informed in the case of abnormal test results. Therapy known to improve psychometric test results should be initiated. (HEPATOLOGY **2004;39:739–745.**)

The prevalence of cirrhosis in the Western world is as high as 1 %.[1,2] Patients with cirrhosis are prone to developing cerebral dysfunction: hepatic encephalopathy (HE). Clinical manifestations of HE include an altered level of consciousness, impaired intellectual functioning, personality changes, and neuromuscular dysfunction.[3] On the basis of clinical findings, HE has been graded into 4 stages of severity, ranging from attention deficits to coma.[4]

Subjects without overt HE may suffer from minimal HE (MHE), also termed subclinical or latent HE.[5–7] The prevalence of this condition ranges from 27%[8] to 75 %,[9] depending on the test procedures used and the severity of the liver disease.[10] There is still no standard procedure to diagnose MHE.[6] The condition is of clinical significance, *i.e.*, it impairs the quality of life.[11,12] In addition, psychometric studies have shown that patients with MHE may be unfit to drive a car.[13,14]

To evaluate the driving fitness in subjects with cerebral dysfunction for reasons other than MHE,[15–18] standardized on-road driving tests have been developed.[19–21] The only published on-road study for testing the driving performance in patients with cirrhosis either with or without MHE did not reveal deficits compared to controls.[22] However, in our previous study on the diagnosis and prevalence of MHE,[10] we observed deficiencies in driving

Abbreviations: HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy; km, kilometers; CCRT: Complex Choice Reaction Test; d, effect size.

From the [1]Department of Psychology, University of Hamburg, Hamburg; [2]Rehabilitation Center Foehrenkamp, Moelln; and [3]Department of Gastroenterology and Endocrinology, Georg August University, Goettingen, Germany.

Received July 10, 2003; accepted December 4, 2003.

Supported by a grant from the Federal Institute for Salaried Employees' Insurance, Germany.

Address reprint requests to: Dr. Christian Wein, Department of Psychology, University of Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany. E-mail: wein@uni-hamburg.de; fax: +49- 40-42838-6591.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20095

a car in some of these patients (self-report or relatives' report). Therefore, we performed a prospective controlled study to investigate the fitness to drive a car of patients with cirrhosis, either with or without MHE, using a standardized on-road-driving assessment designed for patients with brain injury.

Patients and Methods

Sample Size. In a previous controlled study, the prevalence of MHE was 30% in 146 patients with cirrhosis.[10] This investigation showed large effect sizes regarding psychometric measurements for group comparison between patients with cirrhosis and controls. Due to the lack of valid data about the extent of driving limitations in cirrhotic patients, the sample size was calculated on the assumption that the capacity to drive a car and to perform the psychometric tests was equally affected in cirrhotic patients. A power analysis showed that a total sample size of 70, *i.e.*, 35 subjects in each group, was required to conduct the study. However, as the driving impairment in cirrhotic patients could be less frequent than abnormal performance in psychometric tests we decided to increase the number of the test subjects to 50 cirrhotic patients and 50 controls.

Recruitment Criteria and Patient Characteristics. The hospital stay of patients referred to our rehabilitation center is usually 3 weeks. The hospital does not accept emergency cases. Chronically ill patients are treated with the ultimate goal of improving their ability to work. This is accomplished by providing a structured rehabilitation program that includes a diagnostic and therapeutic workup and psychological, physiotherapeutic, and nutritional advice and support. The study was performed during the 3-week rehabilitation program. Since August 1998, all patients with confirmed cirrhosis were tested for MHE and considered eligible for the study based on the following criteria: age from 25 to 65, no overt HE, no renal insufficiency (plasma creatine concentration <200 μmol/L), no insulin-dependent diabetes mellitus, no heart failure from any cause (New York Heart Association class below 2), no history of cancer, no history of disorders of the central nervous system, no psychiatric disorders, normal blood pressure with or without medication, hemoglobin greater than 10 g/dL, and no consumption of psychotropic drugs or alcohol in the past 6 months. Lactulose medication was not changed or discontinued before the psychometric and driving tests.

Driving criteria were as follows: driver's licence for more than 7 years, more than 100,000 kilometers (km; 62,150 miles) driving experience, more than 4,000 km (2,486 miles) in the last year, and regular driving until at least 1 month before the driving test. Cirrhosis was diagnosed on the basis of (1) case history, (2) clinical examination, (3) biochemical, endoscopic, and ultrasound findings, or (4) liver biopsy (18 patients). The Child-Pugh index was used to assess the severity of liver disease.[23]

Of 274 consecutive patients with cirrhosis, 50 met these criteria.

Reasons for excluding 224 cirrhotic patients from the study were the following: lack of consent (51 patients), not enough driving experience (34), no driver's license (26), alcohol intake in the past 6 months (21), overt HE (20), diagnosis of cancer (18; 13 with hepatocellular carcinoma), age outside the limits (1 under 25, 13 over 65), insulin-dependent diabetes mellitus (12), psychiatric or neurological diseases (10), or other causes (18).

Clinical Controls. Fifty patients without history of liver disease and matched for age, gender, and educational background served as controls. With respect to the liver, all displayed normal clinical, biochemical, and ultrasound findings. These subjects were in a stable phase of chronic gastroenterological disease, mainly chronic inflammatory bowel disease. Medical and driving exclusion criteria were the same as for cirrhotic patients.

All participants gave written informed consent. The study was approved by the institutional review board of the Federal Institute for Salaried Employees' Insurance, Germany. Two patients with cirrhosis of the liver and 1 control patient decided during the on-road assessment not to complete the study. Ninety-seven subjects (48 with cirrhosis and 49 controls) underwent the psychometric testing and the driving assessment during the second week of the hospital stay. Sociodemographic and medical characteristics of the 48 cirrhotic subjects included in the study were comparable to the remaining 226 cirrhotic patients from the original 274; the prevalence of MHE in particular was similar.

Assessment of MHE. MHE was diagnosed by a combination of neuropsychological tests. This test combination has a high sensitivity in detecting MHE[10] and is in conformity with the consensus statements of Ferenci et al.[6] All tests are standardized and have norm values based on healthy control groups.

Complex Choice Reaction Test (CCRT; Wiener Determinationsgeraet[24]). The Complex Choice Reaction Test measures the time required to react to 7 different visual and 2 auditory signals by pressing corresponding buttons or corresponding pedals and the correctness of the response. The test includes the presentation of 180 signals in 3 different blocks of 60 signals each at 3 different time intervals (1,582 milliseconds, 948 milliseconds, and 1,078 milliseconds). The number of correct re-

sponses in a defined time interval is counted and expressed as an age-graded norm value.

Digit Symbol Test. This is a subtest of the German adaptation of the Wechsler Adult Intelligence Scale. In this paper and pencil test, numbers from 1 to 9 have to be paired with different nonsense symbols according to a given key. The score consists of the number of squares filled in correctly in 90 seconds and is expressed as an age-graded norm value.

Trail Making Test.[25] This test of complex visual scanning with a motor component requires the person to draw lines to connect consecutively numbered circles (1 through 25) on a work sheet. The amount of time taken to complete the test is measured and transformed into age-graded norm values.

Classification Rules. MHE was diagnosed if test results were: (1) CCRT 1 out of 3 blocks $<$ percentile 3, (2) CCRT 2 or 3 blocks $<$ percentile 7, or (3) CCRT 1 out of 3 blocks $<$ percentile 7 along with Digit Symbol Test or Trail Making Test $<$ percentile 7. The classification strategy is based on the results of the control group and on the results of a previous study.[26] This combination of cutoff scores results in the optimal ratio between true positive classification of MHE in the group of cirrhotic patients and false positive (misclassified) in controls.[26,27]

Assessment of On-Road Driving. The test route of 35 km (22 miles) was designed according to Hartje et al.[19] and covered typical aspects of road traffic (*i.e.*, inner-city area and highway). In addition, time was taken to complete a closed-course track under highly standardized conditions. The duration of the on-road driving assessment, including the closed-course track, was approximately 90 minutes. The driving assessment was performed in the same week as the testing for MHE.

Subjects were assessed in the morning; all drove the same car equipped with a dual-brake system and an indexing gear. Under unfavorable driving conditions (*e.g.*, fog or ice), testing was postponed. A professional driving instructor and a psychologist, both unfamiliar with the subjects′ diagnosis and test results, carried out the evaluation. The assessment was based on behavioral observations in 4 driving categories: car handling, adaptation to traffic situations, cautiousness, and maneuvering the car. The assessment was also based on behavioral observations of specific driving actions: following road signs, paying attention to cyclists and pedestrians, checking in the rearview mirror and the blind spot before changing lanes, tracking, signaling to turn in a timely fashion, following traffic rules, keeping an appropriate distance, being mindful of oncoming traffic, merging smoothly into the flow of traffic, slowing down and/or stopping at construction sites, obeying the speed limit, overtaking, starting on an incline, adjusting speed to road and traffic conditions, changing lanes, parking, and obeying traffic lights. The professional driving instructor used a 6-point rating scale to judge driving competence for each category and action and gave a final score for overall impression (total judgment). The role of the psychologist was to ensure that no information about health status or psychometric test results was given to the driving instructor and to record the number of interventions made by the instructor.

Statistical Analysis. A power analysis based on the 30% prevalence of MHE[10] showed that differences in neuropsychological tests between patients with cirrhosis and a clinical control group have a large effect size ($d > 0.8$). The power analysis carried out with the computer program GPOWER[28] (F. Faul, University Kiel, Germany) resulted in a total required sample size of 70.

All data were analyzed anonymously. Descriptive statistics are given in parametric units (means, SDs). Assumptions for conducting ANOVAs (within-group homogeneity of variances and normal distribution) were not met for several of the dependent variables. Therefore, group differences were analyzed with nonparametric tests. Differences between 2 groups were tested with the Mann-Whitney *U* test; for differences among more than 2 groups, Kruskal-Wallis H was used (ANOVA by ranks). Mann-Whitney *U* tests were performed for *post hoc* comparisons after computing Kruskal-Wallis H. Evaluation of the relationship of dichotomic variables was carried out by Fisher‘s exact test. For all analyses, the results of statistical significance differed only marginally between ANOVAs and nonparametric tests. The limit for statistical significance was set at $P < .05$ (2-tailed testing).

Age-corrected percentiles were used to classify patients with cirrhosis into those with and those without MHE and for comparisons with the clinical control group. A factor-analytic pre-analysis (principle component analysis with varimax rotation) of the driving instructor's rating data, leading to several independent factors, showed that the driving actions were judged multidimensionally, indicating that ratings of different driving actions were independent.

Results

According to the exclusion criteria and neuropsychological classification mentioned above, we diagnosed MHE in 14 of 48 patients with cirrhosis (29%). This prevalence of MHE is similar to the remaining group of patients with cirrhosis: 56 patients with MHE out of 226 patients (25 %). Cirrhotic patients with or without MHE and controls did not differ in age, gender, estimation of IQ, education, and driving experience (Table 1). Patients with and without MHE were comparable in the etiology

Table 1. Sociodemographic and Driving Characteristics of Cirrhotic Patients and Clinical Control Subjects

	Cirrhotic Patients			
	All	MHE+	MHE−	Controls
Gender (F/M)	15/33	3/11	12/22	15/34
Age (y)	49.7 [8.2]	53.0 [6.4]	48.4 [8.7]	49.8 [8.0]
Education (y)	9.8 [1.9]	9.2 [1.9]	10.0 [1.8]	10.2 [2.0]
Estimation of IQ (raw score)	29.7 [3.7]	29 [2.4]	30 [4.1]	29.7 [2.9]
Driving experience (1,000 km/y)	16.2 [11.0]	21.1 [11.3]	14.3 [10.4]	18.6 [12.8]
Driver's license (y)	29.1 [8.5]	33.6 [8.4]	27.4 [8.0]	29.7 [9.0]

NOTE. Values are expressed as mean [SD].

of cirrhosis, the Child-Pugh index,[23] varices, ascites, and levels of aspartate transaminase, total bilirubin, albumin, and prothrombin activity; however, significantly more patients with MHE were on lactulose (Table 2). In the control group of 49 subjects, 2 patients showed psychometric test results below the cutoff score for MHE (false positives).

Rating of Driving Abilities by Driving Instructor. The ratings of the driving instructor revealed significant differences between patients with and without MHE for total judgment and for the driving categories (adaptation to driving situation, cautiousness, and handling the car; Table 3). Driving assessment showed significant differences between patients with and without MHE for the following driving actions: following road signs, paying attention to bicyclists and pedestrians, checking the rearview mirror and the blind spot before changing lanes, tracking, signaling to turn in a timely fashion, and following traffic rules (Table 4).

Time measurements of the performance in the closed-course track showed no significant differences between the groups: with MHE (mean = 34.01 seconds, SD = 4.47 seconds); without MHE (mean = 31.93 seconds, SD = 6.77 seconds; and controls mean = 31.67 seconds, SD = 4.20 seconds).

Severity of cirrhosis (Child-Pugh index), pathogenesis of cirrhosis (alcohol versus other), and medication with lactulose had no influence on any driving category or driving action.

Interventions by the Driving Instructor. In the vast majority of the test subjects, no intervention was necessary; however, in 11 patients, the driving instructor had to intervene 1 or 2 times to avoid accidents. This was indicated by a signal-tone in the car and recorded by the accompanying psychologist. The 3 groups differed significantly with respect to the number of interventions (Table 5). The likelihood of an intervention in patients with cirrhosis and MHE was nearly 10 times higher (8 interventions in 14 driving tests = likelihood .571) than that of cirrhotic patients without MHE (2 interventions in 34 driving tests = likelihood .059). This difference is highly significant (Fisher exact test; P [2-tailed] = .008).

Table 2. Medical Characteristics of Cirrhotic Patients

Characteristics	Cirrhotic Patients MHE+ N = 14	Cirrhotic Patients MHE− N = 34
Etiology		
Alcohol-toxic	10	19
Hepatitis (B, C)	2	3
Autoimmune	1	4
Unknown	1	4
Primary biliary cirrhosis	0	2
Wilson's disease	0	1
Hemochromatosis	0	1
Child-Pugh A/B/C	9/4/1	28/6/0
Esophageal/Gastric varices (yes/no)	10/4	21/13
Ascites		
No	10	30
Mild	2	3
Significant	2	1
Lactulose (yes/no)*	8/6	9/25
Aspartate transaminase (U/L)	18.64 [6.15]	18.79[12.81]
Total bilirubin (μmol/L)	26.25[17.59]	23.15[12.09]
Albumin (g/L)	3.69 [0.68]	4.06 [0.62]
Prothrombin activity (%)	87.43[14.69]	96.71[22.56]

NOTE. Values of Aspartate transaminase, Total bilirubin, Albumin, and Prothrombin activity are expressed as mean [SD].

*Fisher exact test: MHE+ vs. MHE−, P = .04.

Discussion

In this study, patients with MHE showed a diminished ability to drive a car as indicated by the assessment of a professional driving instructor who was not aware of the diagnoses of the patients and the psychometric test results. Based on the total judgment of the driving instructor and the results of the driving categories "car handling," "adaptation," "cautiousness," and "maneuvering," fitness to drive was significantly reduced in patients with MHE compared to clinical controls (Table 3).

As shown in Table 4, the deficits in driving fitness became particularly apparent in 6 specific driving actions:

Table 3. Ratings of Driving Categories

	MHE+		MHE−		Controls				
Categories*	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**H**	***P***	***Post*†**
Total Judgment	3.5	0.9	3.0	0.9	2.7	0.9	9.0	.011	#
Car handling	3.2	1.1	2.5	0.8	2.4	0.8	7.2	.027	+#
Adaptation	3.5	1.0	2.9	1.0	2.7	0.9	7.0	.031	#
Cautiousness	3.6	1.2	3.1	1.2	2.7	0.9	6.9	.033	#
Maneuvering	3.1	1.0	2.6	0.9	2.4	0.8	5.1	.078	#

Abbreviations: H, Kruskal-Wallis H; *P,* level of significance between all groups; *Post*, Mann-Whitney *U* test performed for *post hoc* comparisons.

*Total Judgment = total judgment of the driving instructor; car handling = skillfulness in handling the car; adaptation = adaptation of driving behavior to different traffic situations (flexibility); cautiousness = observation of traffic situation; maneuvering = skillfulness of driving.

†Significant differences between groups: +, MHE+ vs. MHE− significant; #, MHE+ vs. clinical controls significant (in all categories, no differences between MHE− and clinical controls).

following road signs, paying attention to pedestrians and cyclists, checking the rearview mirror before changing lanes, tracking, signaling to turn, and following traffic rules. With regard to a possible explanation, patients with HE exhibit deficits in intelligence, consciousness, behavior, and neuromuscular function.[3] For example, failure to pay the appropriate attention to pedestrians and cyclists may be related to diminished consciousness and neuromuscular function resulting in impaired complex attention and executive function.

An on-road driving evaluation is also a reliable tool for revealing deficits in driving ability in other diseases, such as Alzheimer's and Parkinson's disease, even in the mild to moderate stages.[29,18]

Time measurements in the closed-course track—as a theoretical alternative to the on-road driving assessment—showed no significant differences between the study groups.

Most importantly, however, the driving instructor had to intervene to avoid an accident significantly more often in patients with MHE than in patients without MHE or in controls. The driving assessment in this study was performed under optimal conditions (*e.g.*, good weather, daylight, no time pressure), so the number of driving

Table 4. Ratings of Driving Actions

	MHE+		MHE−		Controls				
Driving Action*	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**H**	***P***	***Post*†**
Road signals	2.93	0.92	1.94	0.81	2.18	0.70	14.27	.001	+#
Bikes/Pedestrians	4.21	0.89	3.06	1.20	3.02	0.95	12.60	.002	+#
Check mirror	4.00	0.88	3.24	1.02	3.04	0.76	12.03	.002	+#
Tracking	2.50	0.65	2.29	0.80	2.02	0.48	8.41	.015	#
Signal	3.43	0.85	2.85	0.86	2.78	0.85	8.48	.018	#
Rules	3.50	1.02	3.12	1.04	2.76	0.75	7.85	.020	#
Distance	2.57	0.94	2.41	0.70	2.16	0.47	5.82	.055	
Oncoming traffic	2.71	0.91	2.15	0.61	2.18	0.60	5.78	.056	+#
Merge	3.21	1.05	2.56	1.11	2.59	0.98	5.42	.067	
Slowing	3.64	0.93	3.06	1.01	3.04	0.82	4.80	.091	
Speed limit	3.64	1.08	3.00	1.13	2.94	0.97	4.67	.097	
Start	2.08	0.95	1.74	0.51	1.96	0.50	4.03	.133	
Overtake	1.77	1.59	1.68	0.98	1.32	0.78	3.93	.140	
Speed	2.93	0.83	3.00	0.98	2.67	0.99	2.94	.229	
Lane	2.36	0.74	2.24	0.61	2.10	0.55	2.38	.305	
Parking	2.43	0.94	2.09	0.67	2.12	0.83	1.77	.412	
Traffic light	2.14	0.53	1.94	0.34	2.08	0.61	1.74	.420	

Abbreviations: H, Kruskal-Wallis H; *P,* level of significance between all groups; *Post*, Mann-Whitney *U* tests performed for *post hoc* comparisons.

*Road signals = following road signs; bikes/pedestrians = paying attention to cyclists and pedestrians; check mirror = checking in rearview mirror and blind spot before changing lanes; signal = signaling to turn in a timely fashion; rules = following traffic rules; distance = keeping an appropriate distance; oncoming traffic = being mindful of oncoming traffic; merge = merging smoothly into the flow of traffic; slowing = slowing down and/or stopping at construction sites; speed limit = obeying the speed limit; start = starting on an incline; speed = adjusting speed to road and traffic conditions; lane = changing lanes; trafic light = obeying traffic lights.

†Significant differences between groups: +, MHE+ vs. MHE− significant; #, MHE+ vs. significant clinical controls (in all actions, no differences between MHE− and clinical controls).

Table 5. Number of Interventions by the Driving Instructor

Patients	No Intervention	One Intervention	Two Interventions
MHE+	9	2	3
%	64	14	22
MHE−	32	2	0
%	94	6	0
Controls	45	3	1
%	92	6	2

NOTE. Patients with cirrhosis and MHE (MHE+) vs. patients with cirrhosis without MHE (MHE−): Fisher exact test, P [2-tailed] = .008.

errors might even be higher in daily life. No differences were found between the groups of cirrhotic patients without MHE and clinical controls in either driving actions or in interventions by the driving instructor. In our study, the number of cirrhotic patients with MHE is limited. However, the medical and sociodemographic variables are comparable in patients with and without MHE: driving fitness is significantly reduced in MHE patients. Thus, MHE, but not cirrhosis *per se*, seems to impair the fitness to drive.

Previous investigators suggested that the ability to drive a car may be compromised in up to 85% of patients with MHE.[13,14] This contention was based on neuropsychological tests only. However, an on-road driving assessment was not performed. The first to use such a test were Srivastava et al.,[22] but they did not detect differences in driving performance between groups of 9 cirrhotic patients with MHE, 6 without MHE, and 15 healthy control subjects. This is not in conformity with our results. The possible reasons for the discrepancy are unclear, but they may include differences in patient selection, in the size of the study group, in diagnosing MHE, and in performing the on-road driving test.

In the present study, 3 psychometric tests (Complex Choice Reaction Test, Digit Symbol Test, and Trail Making Test) were used to diagnose MHE. Because age and education can influence neuropsychological performance,[8,30] patients were carefully matched to the control group. Age and education had no impact on the driving categories or driving actions tested.

The prevalence of MHE in our patient group was 14 out of 48 (29%) when age-adjusted values for psychometric tests were used. A similar proportion was found in a previous study performed at our hospital[10] and in studies from other investigators.[8,31,32] Srivastava et al.[22] found abnormal neuropsychological results in 60% of their patients.

With regard to patient selection, Srivastava et al. excluded patients with liver cirrhosis and a history of overt encephalopathy.

A further reason why we detected deficits in driving performance could be due to the fact that the professional driving instructor assessed our patients for a longer period of time than Srivastava et al.[22]—90 minutes instead of 30 minutes with highly specified driving actions on an extremely standardized driving course.

Thus, MHE is a condition that may diminish the ability to drive. As a consequence, we feel justified in endorsing surveillance and treatment of these patients but are not yet to conclude that all of them are unfit to drive. One reason is the lack of data indicating a higher number of traffic accidents caused by patients with MHE. Nevertheless, any patient with MHE should be informed about this possible risk. Whether anti-encephalopathy therapy[33–37] will improve driving abilities in MHE patients is not known. We suggest that this problem should be submitted to a clinical trial. Furthermore, we strongly recommend studies to answer the question of whether cirrhotic patients are actually causing more car accidents or traffic violations as a result of MHE.

References

1. Bellentani S, Tiribelli C, Saccoccio G, Sodde M, Fratti N, De Martin C, Cristianini G. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. HEPATOLOGY 1994;20:1442–1449.
2. Dufour MC, Stinson FS, Caces MF. Trends in cirrhosis morbidity and mortality: United States, 1979-1988. Semin Liver Dis 1993;13:109–125.
3. Butterworth RF. Pathogenesis and treatment of portal-systemic encephalopathy: an update. Dig Dis Sci 1992;37:321–327.
4. Parsons-Smith BC, Sumerskill WHJ, Dawson AM. The electroencephalograph in liver disease. Lancet 1957;273:867–871.
5. Gitlin N. Subclinical portal-systemic encephalopathy. Am J Gastroenterol 1988;83:8–11.
6. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy— definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. HEPATOLOGY 2002;35:716–721.
7. Blei AT. Diagnosis and treatment of hepatic encephalopathy. Baillieres Best Pract Res Clin Gastroenterol 2000;14:959–974.
8. Quero JC, Hartman IJ, Meulstee J, Hop WCJ, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. HEPATOLOGY 1996;24:556–560.
9. Sood GK, Sarin SK, Mahaptra J, Broor SL. Comparative efficacy of psychometric tests in detection of subclinical hepatic encephalopathy in nonalcoholic cirrhotics: search for a rational approach. Am J Gastroenterol 1989;84:156–159.
10. Koch H, Schauder P, Schafer G, Dahme B, Ebel W, Vahldiek B, Konig F, et al. [Diagnosis and prevalence of latent hepatic encephalopathy]. Z Gastroenterol 1990;28:610–615.
11. Groeneweg M, Quero JC, De Bruijn I, Hartmann IJ, Essink-bot ML, Hop WC, Schalm SW. Subclinical hepatic encephalopathy impairs daily functioning. HEPATOLOGY 1998;28:45–49.
12. Groeneweg M, Quero JC, Essink-Bot ML, Hop WCJ, Schalm SW. The effect of subclinical hepatic encephalopathy on the quality of life. In: Record C, Al-Mardini H, eds. Advances in Hepatic Encephalopathy and Metabolism in Liver Disease. Newcastle upon Tyne, UK: Ipswich, 1996: 311–317.
13. Watanabe A, Tuchida T, Yata Y, Kuwabara Y. Evaluation of neuropsychological function in patients with liver cirrhosis with special reference to their driving ability. Metab Brain Dis 1995;10:239–248.

14. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Dolle W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981;26:622–630.
15. Schultheis MT, Matheis RJ, Nead R, DeLuca J. Driving behaviors following brain injury: self-report and motor vehicle records. J Head Trauma Rehabil 2002;17:38–47.
16. Schultheis MT, Garay E, DeLuca J. The influence of cognitive impairment on driving performance in multiple sclerosis. Neurology 2001;56:1089–1094.
17. Hannen P, Hartje W, Skreczek W. [Evaluating driving ability after brain damage. Neuropsychological diagnosis and driving test]. Nervenarzt 1998; 69:864–872.
18. Heikkila VM, Turkka J, Korpelainen J, Kallanranta T, Summala H. Decreased driving ability in people with Parkinson's disease. J Neurol Neurosurg Psychiatry 1998;64:325–330.
19. Hartje W, Pach R, Willmes K, Hannen P, Weber E. Fahreignung hirngeschaedigter patienten. [Driving competence of brain injured patients]. Z f Neuropsych 1991;2:100–114.
20. Fox GK, Bashford GM, Caust SL. Identifying safe versus unsafe drivers following brain impairment: the Coorabel Programme. Disabil Rehabil 1992;14:140–145.
21. Fox GK, Bowden SC, Smith DS. On-road assessment of driving competence after brain impairment: review of current practice and recommendations for a standardized examination. Arch Phys Med Rehabil 1998;79: 1288–1296.
22. Srivastava A, Mehta R, Rothke SP, Rademaker AW, Blei AT. Fitness to drive in patients with cirrhosis and portal-systemic shunting: a pilot study evaluating driving performance. J Hepatol 1994;21:1023–1028.
23. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646–649.
24. Berg M, Fischer A. Wiener Determinationsgeraet Version 6.0. Vienna: Dr. G. Schuhfried GmbH, 1994.
25. Schomerus H, Weissenborn K, Hamster W, Rueckert N, Hecker H. PSE-Syndrom-Test. Frankfurt: Swets & Zeitlinger, 1999.
26. Wein C. Subclinical hepatic encephalopathy - development and evaluation of a computer-assisted test for psychometric diagnosis [dissertation]. Hamburg: Psychological Institute, 1996.
27. Bruggemans EF, Van de Vijver FJ, Huysmans HA. Assessment of cognitive deterioration in individual patients following cardiac surgery: correcting for measurement error and practice effects. J Clin Exp Neuropsychol 1997; 19:543–559.
28. Erdfelder E, Faul F, Buchner A. GPOWER: A general power analysis program. Behav Res Methods Instrum Comput 1996;28:1–11.
29. Fox G K, Bowden SC, Bashford GM, Smith DS. Alzheimer's disease and driving: prediction and assessment of driving performance. J Am Geriatr Soc 1997;45:949–953
30. Zeneroli ML, Cioni G, Ventura P, Russo AM, Venturini I, Casalgrandi G, Ventura E. Interindividual variability of the number connection test. J Hepatol 1992;15:263–264.
31. Amodio P, Del Piccolo F, Marchetti P, Angeli P, Iemmolo R, Caregaro L, Merkel C, 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;29:1662–1667.
32. Weissenborn K, Scholz M, Hinrichs H, Wiltfang J, Schmidt FW, Kunkel H. Neurophysiological assessment of early hepatic encephalopathy. Electroencephalogr Clin Neurophysiol 1990;75:289–295.
33. Egberts EH, Schomerus H, Hamster W, Jurgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. A double-blind placebo-controlled crossover study. Gastroenterology 1985;88:887–895.
34. Morgan MY, Alonso M, Stanger LC. Lactitol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. A randomised, cross-over study. J Hepatol 1989; 8:208–217.
35. Plauth M, Egberts EH, Hamster W, Torok M, Muller PH, Brand O, Furst P, et al. Long-term treatment of latent portosystemic encephalopathy with branched-chain amino acids. A double-blind placebo-controlled crossover study. J Hepatol 1993;17:308–314.
36. Watanabe A, Sakai T, Sato S, Imai F, Ohto M, Arakawa Y, Toda G, et al. Clinical efficacy of lactulose in cirrhotic patients with and without subclinical hepatic encephalopathy. HEPATOLOGY 1997;26:1410–1414.
37. Dhiman RK, Sawhney IM, Chawla Y, K., Das G, Ram S, Dilawari JB. Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy. Dig Dis Sci 2000;45:1549–1552.