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Cognitive impairment in people diagnosed with end-stage liver disease evaluated for liver transplantation

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Abstract Cognitive impairments are common in patients with end-stage liver disease (ESLD). The aim of the present study was to identify and characterize the neuropsychological deficits between groups of patients with a variety of causes of ESLD and to assess the impact of heavy alcohol use on cognitive functioning. Cognitive functioning in 300 consecutive outpatients presenting for liver transplantation evaluation was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). All patients underwent a psychiatric interview and a physical and laboratory assessment. The prevalence of neuropsychological impairment was highest among patients with liver disease secondary to alcohol. Poor performance on neuropsychological testing was correlated strongly with the severity of liver disease as measured by the model for end-stage liver disease (MELD). After controlling for the linear effects of MELD in subsequent analysis, a group difference emerged in patients with cholestatic liver disease showing less cognitive impairment when compared to all other groups. After controlling for the severity of liver disease, those patients with a history of alcohol abuse or dependence were found to perform more poorly on neuropsychological testing than those patients without such a history. Furthermore, the presence of these cognitive impairments predicted disability independent of the severity of the underlying liver disease.

Key words alcoholism, cholestatic liver disease, cirrhosis, hepatic encephalopathy, neuropsychological impairment.

INTRODUCTION

Patients with end-stage liver disease (ESLD) are vulnerable to cognitive dysfunction. Clinical presentation and pathophysiologic mechanisms of brain injury are dependent on the type of liver failure (fulminant vs chronic), and chronic liver disease may present with a clinical spectrum ranging from rapidly developing acute confusion and coma to persistent and progressive cognitive impairments fully appreciated only on psychometric testing. This cognitive impairment noted in the presence of a clear sensorium is often referred to as subclinical hepatic encephalopathy and more recently minimal hepatic encephalopathy (MHE). Diagnosis relies on either evidence from psychometric testing or electrophysiological measures such as evoked potentials and spectral electroencephalography.[1,2] Nevertheless, enthusiasm in clinical practice to identify those patients with more subtle forms of encephalopathy is muted by an incomplete understanding of the impact of these deficits on functioning and well-being, the lack of ease of assessment, and the limited effectiveness of current treatment strategies.

The pattern of impairments associated with MHE appears to be subcortical and as such affects attention, motor speed, as well as affective and executive functioning.[3,4] The effects of encephalopathy, especially MHE, on quality of life and outcomes in patients prior to and following transplant are significant, yet incom-

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pletely understood. A recent study in 160 patients with cirrhosis found that hepatic encephalopathy (HE) and MHE had detrimental effects on a health-related quality of life measure.[5] Furthermore, despite initial enthusiasm that transplantation would correct this syndrome,[6] evidence is accumulating that suggests the persistence of these cognitive impairments following liver transplantation.[7]

Neuropsychological impairments are frequently observed in patients presenting for a liver transplant evaluation and several attempts to characterize and quantify these impairments are in the literature. One study provided neuropsychological data in the form of four subtests on an intelligence test in a group of patients being evaluated for liver transplantation.[8] Their findings revealed overall cognitive functioning in the normal range for their measure of language, arithmetic, digit span and in the low-average range for block design. Importantly, cognitive performance was negatively correlated with liver disease severity (Child–Pugh score). The majority of patients in that study had hepatitis C (59%) and the impact of etiology of liver disease was not assessed. Amodio *et al*. also reported on the cognitive performance on tasks of sustained attention and choice reaction times in approximately 20% of 94 cirrhosis patients compared to controls.[9] In that study the influence of liver disease severity was not addressed.

Alcohol has often been implicated in cognitive impairments in individuals without liver disease although the findings are inconsistent and often believed to resolve following detoxification. Previous studies with cirrhosis patients have attempted to find a difference in the frequency of impairments in patients with alcohol-induced versus other etiologies of liver disease. Tarter *et al*. reported the results of extensive cognitive testing across a very broad array of neuropsychological domains.[10] They found no significant differences between 24 men with alcohol-related cirrhosis and 26 men with cirrhosis not related to alcohol, except for poorer performance on the Trail-Making Test B. Severity of liver disease was not assessed in their analysis. The same group reported similar deficits in a cohort of 13 alcohol-related cirrhosis patients that showed substantial but incomplete recovery 1 year following transplantation.[11] A more recent study by Edwin *et al*., also utilizing comprehensive measures of neuropsychological domains and a larger sample size ($n = 169$), contrasted performance of patients with alcohol-induced cirrhosis versus patients with other forms of liver disease.[12] After controlling for severity of liver disease with Child–Pugh scores, they found no greater incidence of cognitive impairment in the alcohol-related group than the group with liver disease of other etiology. One potential limitation of all of these studies is the use of the diagnosis of alcoholic liver disease as a proxy for a history of alcoholism, and the attendant assumption that those with cirrhosis clinically judged to be unrelated to alcohol do not, in fact, have a history of heavy drinking. In other words the aforementioned studies did not independently assess the alcohol histories of patients across groups.

Chronic hepatitis C infection is the most common cause of chronic liver disease and the leading indication for transplantation in the USA. Recently, evidence has emerged that the hepatitis C virus can be found in the central nervous system and may have a role in a subcortical pattern of neuropsychological impairment in patients with hepatitis similar to that seen in HIV/AIDS dementia.[13,14] Similar work in patients with more advanced liver disease (i.e. cirrhosis) has not been reported.

The present study is an assessment of cognitive functioning in a large sample of adult outpatients with ESLD presenting for liver transplantation evaluation. We were interested in the prevalence of cognitive impairment across groups defined by etiology of ESLD. We theorized that the presence of cognitive impairments affected overall functioning of these patients independent of the severity and etiology of liver disease. In contrast to prior studies, we utilized the model for end-stage liver disease (MELD) to assess and control for severity of liver disease. The MELD score is used to assess severity and urgency of patients awaiting liver transplant. It is calculated by using a formula involving three routine laboratory test results: serum creatinine, total bilirubin and international normalized ratio (INR). We were also interested in assessing the impact of a history of heavy alcohol use and chronic hepatitis C infection on neuropsychological performance in all patients independent of etiology and severity of liver disease. And finally, we assess the utility of a brief measure of neuropsychological performance, sensitive to both subcortical and cortical deficits, in this patient population.

METHOD

Subjects

We evaluated all consecutive adult outpatients with ESLD who presented for orthotopic liver transplantation evaluation at the University of Nebraska Medical Center. The mean age of the patients was 50.07 ± 9.38 years (range, 18.52–71.82 years), 175 were male and attained an average education of 13.12 ± 2.54 years (Table 1). A total of 233 were white, 18 were Hispanic, 15 were Native American, 10 were

Table 1. Demographics and clinical measures by etiology

Measure	HCV ($n = 75$)	ALD+C ($n = 46$)	ALD ($n = 46$)	CLD ($n = 32$)	OLD ($n = 81$)	P
Age (yeasr)	50.99 ± 6.83	49.83 ± 6.96	52.18 ± 7.31	48.64 ± 10.29	48.74 ± 12.62	0.243
Education (years)	13.00 ± 2.47	12.04 ± 2.00	12.63 ± 2.05	14.56 ± 2.90	13.56 ± 2.68	<0.001
Male : Female (n)	44:31	40:6	34:12	14:18	43:38	0.002
MELD	13.41 ± 5.80	15.02 ± 3.76	17.76 ± 8.88	13.66 ± 6.87	14.69 ± 6.62	0.008
Caucasian (n)	60	39	38	28	68	0.820
Disabled (n)	36	29	30	7	38	0.150
Alcohol abuse/ dependence (n)	25	45	45	4	17	<0.001
Substance abuse/ dependence (n)	25	25	5	1	3	<0.001

ALD, alcoholic liver disease; ALD+C, alcoholic liver disease and hepatitis C; CLD, cholestatic liver disease; HCV, hepatitis C virus; MELD, model for end-state liver disease; OLD, other liver disease.

Comparisons on continuous variables were computed with ANOVA, and categorical variables were analyzed with χ^2.

African–American and four were from other ethnic groups. Forty-six had alcoholic liver disease (ALD), another 46 had alcoholic liver disease and hepatitis C (ALD+C), 75 had liver disease due to hepatitis C virus (HCV), 32 had cholestatic liver disease (CLD) and another 81 had other causes of liver disease, either non-alcoholic steatohepatitis, cryptogenic cirrhosis or other diseases including hepatomas and α-1 antitrypsin deficiency (OLD). Three hundred patients were evaluated between January 2002 and February 2004. Twenty patients whose neuropsychological functioning was determined to be the result of learning disability, neurosurgery, dementia, Parkinson's disease, multiple seizures, multiple closed-head injuries, inadequate effort, non-compliance with testing or severe confusion during testing were excluded from the present study.

Clinical and laboratory evaluation

All patients who presented for liver transplantation evaluation underwent a comprehensive, multidisciplinary assessment of their physical, psychiatric, neuropsychological and social status, which yielded information regarding age, gender, educational attainment, employment status, neuropsychological status, neuropsychiatric status, liver disease etiology, liver disease severity, physical functioning, medical history, and treatment status. All patients were evaluated by a hepatologist, transplant surgeon, psychiatrist, clinical psychologist and social worker. Patients underwent detailed physical examination and a semistructured psychiatric interview. Diagnoses of alcohol abuse and dependence as well as substance abuse and dependence were made by psychiatrists using DSM IV-TR criteria.[15] Biochemical evaluation included serum chemistries and urinalysis as well as urine drug screen. Average MELD score was 14.79 ± 6.63. Analysis of variance (ANOVA) indicated that there was a significant difference in MELD scores between etiologies, $F(4278) = 2.86$, $P = 0.024$. Post-hoc analyses utilizing least significant difference (LSD) methods revealed that those with ALD had a significantly higher MELD score relative to those with HCV ($M_{diff} = 4.36$) and those with CLD ($M_{diff} = 4.11$). All evaluations and biochemical tests were performed within a 1-week period.

Neuropsychological testing

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[16] was administered to each patient in conjunction with the Trail-Making Test[17] and a cognitive history evaluation to yield information regarding a broad range of neuropsychological functioning and the likely cause of any neuropsychological impairment. All tests were administered during the same week as the clinical evaluations and biochemical tests. The RBANS is a brief neuropsychological test developed primarily for the detection of dementia, and yields information regarding neuropsychological functioning across five domains including immediate memory, delayed memory, visuospatial/constructional ability, language, and attention. The RBANS has been shown to be effective in detecting and characterizing cognitive impairments of various etiologies, both cortical and subcortical.[18–20] The RBANS index scores are adjusted for age and education to allow comparisons across groups. A higher score reflects better cognitive performance (Table 2).

The Trail-Making Test yields two reaction times: Trails A or the time it takes an individual to connect 25 numbered circles in sequence (e.g. connect 1–2, then 2–3); Trails B or the time it takes an individual to connect

Table 2. RBANS domains

Domain	Subtests	Measures
Immediate memory	List learning; story memory	Recall of information immediately after it is presented
Visuospatial/ constructional†	Figure copy; line orientation	Perception of spatial relations; construction of a spatially accurate copy of a drawing
Language‡	Picture naming; semantic fluency	Verbal response to naming or retrieving learned material
Attention†	Digit span; coding	Manipulate and remember both visual and auditory information
Delayed memory‡	List recall; list recognition; story recall; figure recall	Recall of information following a delay in presentation

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.
†Subcortical; ‡cortical.

Table 3. Mean ± SD reaction times of Trails A and B, and RBANS index scores by etiology

Measure	ALD+C	HCV	ALD	CLD	OLD
Trails A (s)	43.00 ± 27.07	35.03 ± 14.51	48.20 ± 24.54	28.38 ± 8.73	36.32 ± 14.89
Trails B (s)	123.72 ± 76.85	104.23 ± 61.66	147.50 ± 92.72	83.41 ± 38.11	108.81 ± 61.55
Immediate memory	87.20 ± 17.91	88.67 ± 15.62	86.76 ± 15.91	97.53 ± 17.75	89.80 ± 14.84
Visuospatial/Constructional	87.65 ± 16.78	90.09 ± 16.99	81.93 ± 18.18	92.84 ± 22.02	89.43 ± 19.62
Language	91.20 ± 8.25	91.91 ± 8.55	88.33 ± 9.57	96.31 ± 8.30	91.04 ± 11.46
Attention	84.98 ± 15.17	86.00 ± 14.65	83.24 ± 18.41	94.16 ± 16.62	82.70 ± 17.82
Delayed memory	91.37 ± 14.31	91.39 ± 13.77	90.91 ± 11.88	95.38 ± 14.44	93.38 ± 11.82
RBANS total	84.74 ± 13.02	85.89 ± 11.67	82.04 ± 13.49	93.38 ± 13.69	85.81 ± 14.05

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

25 numbered and lettered circles in sequence (e.g. connect 1 to A, then A to 2, then 2 to B). Reaction times on the Trail-Making Tests increase with cognitive impairment.

Statistical analysis

Following approval from the Institutional Review Board at the University of Nebraska Medical Center (the committee assigned to review compliance with the Declarations of Helsinki in 1995 and revised in Edinburgh in 2000), all data including demographics, etiology of liver disease, comorbid medical illness, psychiatric status, medications, functional status, alcohol and substance use histories, MELD scores and results of neuropsychological assessment were input into SPSS, version 11.5 (SPSS, Chicago, IL, USA). Descriptive statistics are reported in parametric units (mean ± SD). Five patient groups were created based on etiology of underlying liver: ALD, ALD+C, HCV, CLD, and OLD. Distributions of all continuous variables were tested for normality and no significant skewness or kurtosis was observed. Group differences for continuous variables were evaluated by ANOVA and analysis of covariance (ANCOVA). Cognitive impairment is defined as performance <2 SD below age- and education-matched norms previously established for the RBANS.

RESULTS

Results of neuropsychological tests for all groups are presented in Table 3. There was a striking amount of neuropsychological impairment found in the present sample. Figure 1 gives the percentages of patients for each group who performed 2 SD below age- and education-matched norms on each of the tests. The pattern of neuropsychological impairment indicated a subcortical neuropathology because most striking impairments were in areas of attention, immediate memory, visuospatial construction, with relative preservation of more cortical neuropsychological domains of language and delayed memory. Alcoholic liver disease patients as a group did significantly poorer on testing. This group nonetheless had significantly higher MELD scores indicating worse liver disease, therefore we were

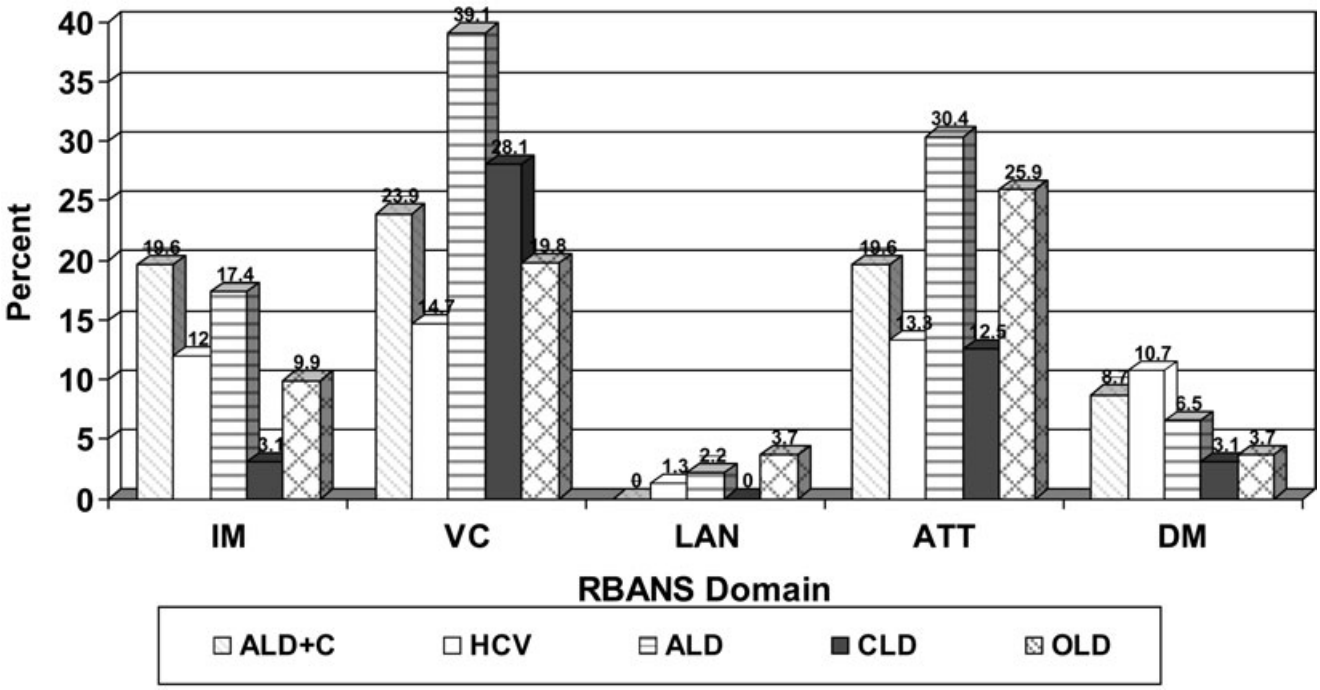

Figure 1. Percent of Neuropsychological Impairment* for Different Liver Disease Groups. *Neuropsychological impairment defined as 2 standard deviations below the mean of age-matched standardized sample.

interested in whether the severity of the liver disease itself was associated with worsening scores and could account for the group differences.

Table 4 demonstrates the strong correlation of liver disease severity with neuropsychological performance. As the MELD increases, cognitive performance on the Trail-Making Tests and on the Visuospatial Construction and Attention tests of the RBANS declined significantly. Subsequently, ANCOVA analysis revealed a significant mean difference between RBANS total index score and different etiologies of liver disease after controlling for MELD, $F_{4,276} = 3.047$, $P = 0.018$. Post-hoc analyses (LSD) indicated that the cholestatic group differed significantly ($P < 0.01$) from all other etiologies. The cholestatic group exhibited significantly less cognitive impairment relative to all other etiologies. In contrast, as noted in the literature, the poor performance by patients with alcoholic liver disease compared to other patients disappeared after controlling for MELD.

As a component of the transplant evaluation, alcohol and drug histories for all patients were obtained regardless of underlying etiology of liver disease. Not surprisingly, almost all the patients with alcoholic liver disease (with or without hepatitis C) had a lifetime history of alcohol abuse or dependence. The groups with hepatitis C had a rate of 33% and of those with ESLD from other causes, 21% still met criteria for abuse or dependence. The lowest alcohol abuse or dependence rates were found in the group with cholestatic liver disease (12%). The effects of alcohol use history on cognitive functioning, after controlling for MELD, were examined by contrasting the RBANS total index and the Trails A and B scores between those without extensive alcohol use history and those who met criteria for past abuse or dependence utilizing DSM IV-R criteria. Results from ANCOVA analyses revealed significant differences in all three measures ($P < 0.01$). Overall, those without extensive alcohol use histories

Table 4. Pearson correlations between MELD, TMT and RBANS index scores

Variables	Correlation coefficient
Reaction time TMT A (s)	0.236**
Reaction time TMT B (s)	0.197**
Immediate memory	–0.063
Visuospatial/constructional	–0.202**
Language	–0.174**
Attention	–0.220**
Delayed memory	–0.052
RBANS total	–0.200**

MELD, model for end-stage liver disease; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; TMT, Trail-Making Test.

**Correlation is significant at the 0.01 level (2-tailed).

Table 5. Correlations between cognitive tests and employment status after controlling for MELD ($n = 235$)

Variables	Correlation coefficients
Reaction time TMT A (s)	0.165*
Reaction time TMTB (s)	0.123
Immediate memory	–0.211**
Visuospatial/Constructional	–0.118
Language	–0.147*
Attention	–0.200**
Delayed memory	–0.084
RBANS total	–0.218**

MELD, model for end-stage liver disease; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; TMT, Trail-Making Test.

*Correlation is significant at the 0.05 level (twotailed); **significant at the 0.01 level (two-tailed).

performed significantly better on the RBANS total index ($M_{diff} = 4.97$, $\eta^2 = 0.028$), Trails A ($M_{diff} = 8.40$, $\eta^2 = 0.039$), and trails B ($M_{diff} = 21.25$, $\eta^2 = 0.029$).

Finally, the impact of neuropsychological impairment on the ability to work was examined by ANCOVA analysis. After controlling for severity of liver disease, a significant difference, $F(1,238) = 11.80$, $P = 0.001$, $\eta^2 = 0.05$, in global RBANS scores was found between those who were disabled ($n = 139$) and those who were currently working outside the home ($n = 99$). Those who were currently working had significantly higher global RBANS scores relative to those who were disabled after controlling for the effects of MELD scores (Table 5).

DISCUSSION

The present study demonstrates significant cognitive impairments for a sample of outpatients with ESLD who presented for liver transplantation evaluation. Overall the major effect was related to severity of liver disease. This is the first study in the literature to report this relationship utilizing MELD instead of Child–Pugh scoring. The strength of this finding was preserved despite concern that the effect previously reported was related to the fact that encephalopathy itself is a criterion for Child–Pugh scoring and therefore potentially confounding. One surprising difference was that after controlling for disease severity, the group with cholestatic liver disease showed significantly less encephalopathy than all other groups. In the only other cognitive assessment of patients with primary biliary cirrhosis (PBC), 36 patients with PBC performed in the normal range and comparably to patients with rheumatoid arthritis on a battery of cognitive tests, although there was a trend towards a decline in orientation and personal memory in those patients included in the study with more histologically severe disease.[21] But the Floreani *et al.* sample was a group of patients with relatively mild liver disease and the suspicion of encephalopathy was cause for exclusion from the study. It is unclear why this group in the present study had relative preservation of their cognitive functioning. Possibly it relates to lifestyle and health-care practices as these patients appear as a whole to be less risk-taking and to prioritize health concerns. More likely it may represent a difference in their MELD.

Despite recent evidence of cognitive impairment of a subcortical nature in patients with hepatitis C infection without severe fibrosis, we found no significant differences between groups with and without hepatitis C on measures of neuropsychological performance. Similarly, a history of substance abuse or dependence did not correlate with poor cognitive performance.

The group with liver disease due to alcohol had the highest rates of impairments on neuropsychological testing. They also had the more severe liver disease as measured by MELD. As previously reported by other researchers, our re-analysis of cognitive testing after controlling for liver disease severity resulted in similar performance on testing for the ALD group versus the other groups (excluding the CLD group). Our clinical experience with patients with ESLD suggested that alcohol misuse was not confined to the group with alcoholic liver disease. We were not surprised to find high rates among patients with hepatitis C because this trend has been previously reported in the literature.[22] We were somewhat surprised to find higher rates than the general population in all groups except those with cholestatic liver disease. The effect of a history of alcohol dependence and alcohol abuse after controlling for disease severity on neuropsychological performance was significant and predicted poorer performance regardless of the etiology of the underlying liver disease. We believe this is a more accurate assessment because earlier studies utilized the diagnosis of alcoholic liver disease as a proxy for alcoholism and assumed that patients in their control groups lacked a history of heavy use. Further work utilizing neuropsychological testing and physiological measures such as functional neuroimaging and molecular studies is necessary to elucidate the mechanism of these group differences. Longitudinal studies on patients with more quantified assessment of alcohol use are necessary to evaluate whether or not cognitive recovery is suboptimal in patients with a history of alcoholism.

Cognitive impairment, especially of a subcortical nature, may substantially diminish the quality of life

and functional capacities of patients with ESLD. In the present study the presence of minimal hepatic encephalopathy predicted disability among patients who had a work history independent of liver disease severity. In a study recently published, driving impairments were noted in a group of patients with MHE.[23] Subcortical cognitive impairments can be relatively subtle and can easily escape clinical attention because language and memory are relatively preserved compared to other neuropsychological domains that can profoundly affect attention, motor performance and decision making. Furthermore, subcortical injury can contribute to depression, apathy and fatigue, which are present in high rates in this patient group, and deserves further study. Additionally, further study is necessary to evaluate whether or not these deficits persist following transplantation and, if so, the impact on functioning and quality of life.

Although a step forward, several limitations exist in the present study. First, a more quantified assessment of alcohol and substance abuse/dependence with more stress on quantity and lifetime history could have been utilized. Second, a superior measure of disability assessment such as the Karnofsky performance scale was lacking. Finally, the cross-sectional nature of the study, with no premorbid neuropsychiatric testing and relying on education as a proxy for intelligence, could be a limiting factor.

It is becoming increasingly clear that MHE is a significant clinical problem that needs to be addressed not only by transplant physicians, but by hepatologists as a whole. Our current study demonstrates high rates among a group of outpatients being evaluated for liver transplantation. This cognitive impairment is related to the severity of liver disease and there is an independent effect of a lifetime history of heavy alcohol use on poor cognitive performance. The presence of these cognitive impairments predicts disability status, again independent of the severity of liver disease. One major obstacle to the identification and optimal treatment of MHE has been the difficulty of diagnosis. We believe that the RBANS is a relatively quick and reliable measure that deserves widespread usage in this population. Furthermore, adopting a standardized, practical and repeatable measurement tool such as the RBANS will aid in the assessment of treatment effectiveness and facilitate multicenter longitudinal studies of cognitive function following liver transplantation.

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