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Original Research

Verbal memory is impaired in patients with cirrhosis

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Abstract

Background: Sub-clinical hepatic encephalopathy is a commonly recognized cognitive sequelae of cirrhosis and is associated with normal neurological and mental status exams but impaired performance on neuropsychological measures. Cognitive slowing and impairments in executive functioning are frequently noted; however, there is debate in the literature regarding the degree of memory dysfunction in patients with sub-clinical hepatic encephalopathy. This study aimed to evaluate memory functioning in patients with sub-clinical hepatic encephalopathy. Method: Individuals with cirrhosis and no overt hepatic encephalopathy who presented for assessment for possible liver transplant to a large academic medical center in the South between January 2002 and July 2003 were randomly selected for analysis. In this retrospective analysis, a sample of convenience of 125 individuals comprised the three diagnostic categories: alcohol (ETOH) induced- (n=40), hepatitis C virus (HCV) without ETOH induced- (n=42), and non-ETOH/non-HCV induced-cirrhosis (n=43). Results: Forty-eight percent of study sample reported difficulties with memory functioning within the past year, independent of disease etiology. Compared to normative data, individuals with all three cirrhosis etiologies performed significantly worse than their healthy peers across neuropsychological measures of verbal memory functioning. Multivariate analyses revealed that individuals with ETOH-induced cirrhosis performed significantly worse than individuals with non-ETOH/non-HCV-induced cirrhosis on a specific measure of learning and memory. Conclusions: Cirrhosis is associated with impaired memory functioning regardless of underlying liver disease etiology. It appears that that sustained periods of excessive ETOH consumption result in greater impairments in memory functioning than hepatic insufficiency alone. Impairments in memory functioning among individuals with cirrhosis have the potential to negatively affect receipt of medical information, compromising compliance with treatment recommendations and negatively affecting pre- and post-transplantation outcomes.

INTRODUCTION

Hepatic encephalopathy (HE) and a sub-clinical variant (SHE) are commonly recognized cognitive sequelae of cirrhosis [1,2]. The hallmark of overt HE is a fluctuation in consciousness (i.e., delirium); whereas, SHE typically is evident within the context of normal neurological and mental status exams [3,4]. However, individuals with SHE evince impaired performance on neuropsychological tests of psychomotor speed, short-term memory/attention, visuospatial perception and construction, and executive functioning compared to healthy controls [5-7]. The cognitive deficits associated

with SHE are characteristic of neuropsychological conceptualizations of subcortical dysfunction [8]. Neurophysiological studies [9] and a variety of brain imaging techniques, including positron emission tomography [10], magnetic resonance imaging [11], and magnetic resonance spectroscopy [12], provide support for subcortical involvement underlying SHE. The cognitive deficits, however, are unlikely to be a consequence of structural changes in brain morphology [13]. Rather they are likely a byproduct of hepatic insufficiency. Most theories of the pathogenesis of HE and SHE implicate the liver's failure to remove nitrogenous substances and other neurotoxins from the plasma, thus indirectly affecting central nervous system (CNS) functioning [1, 14, 15].

Despite the well-established consequence of subcortical impairment on memory functioning [8], the literature to date in the area of cognitive functioning and cirrhosis has inconclusively implicated memory dysfunction as a characteristic of SHE. Some researchers have reported impaired memory functioning [4, 16-19], while others have reported intact functioning [6, 20, 21]. Additionally, Laennec's (alcoholic) cirrhosis is a common etiology of cirrhosis, and the consequence of excessive alcohol consumption on memory functioning is well established [22]. Thus, the lack of consensus in the literature regarding memory impairments associated with cirrhosis is surprising.

Because memory functioning consists of three primary processes: an initial encoding stage, a consolidation phase, and a retrieval phase, observed deficits in delayed recall of information can be the result of dysfunction in one or more of these primary processes [23]. Encoding and retrieval are usually associated with deficits in attention and/or executive functioning – areas of cognitive impairment that are associated with subcortical involvement [8] and consistently are implicated in SHE [6, 7]. Thus, we hypothesized that verbal memory dysfunction would be evident across neuropsychological measures regardless of the etiology of cirrhosis, given our understanding of the impact of subcortical dysfunction on memory. Additionally, we hypothesized that verbal memory dysfunction would be greater among individuals with alcohol-induced cirrhosis relative to the other major cirrhosis etiologies, because of the former's direct effects on CNS functioning in addition to the indirect consequences of hepatic insufficiency.

METHODS

Participants

One hundred twenty-five (N=125) individuals with cirrhosis and without overt HE were randomly selected for analyses. Each participant presented for assessment for possible liver transplantation to the University of Alabama at Birmingham's Liver Center between January 2002 and July 2003. In this sample of convenience, three etiologic groups were represented: alcohol-induced (ETOH; n=40), hepatitis C-induced (HCV; n=42), non-alcohol/non-HCV-induced (OTHER; n=43) cirrhosis. The following disease etiologies were included in the OTHER diagnostic category: hepatitis B, autoimmune hepatitis, alpha-1-antitrypsin deficiency, primary sclerosing cholangitis, primary biliary cirrhosis, secondary sclerosing cholangitis, fibropolycystic liver disease, nonalcoholic steatohepatitis, hemachromatosis, Wilson's disease, cryptogenic cirrhosis, Budd-Chiari syndrome, amyloidosis, and sarcoidosis. Data collection and analyses were conducted with full approval from the Institutional Review Board of the University of Alabama at Birmingham.

Procedure

In this retrospective analysis, individual medical records were reviewed. The records included a completed clinical diagnostic interview, a questionnaire assessing depressive symptomatology, a comprehensive neuropsychological assessment, and medical history, which included laboratory findings.

Dependent Measures

Verbal memory functioning was operationalized as performance on the California Verbal Learning Test – Second Edition (CVLT-II) [24] and the Logical Memory I and II subscales (LM1 and LM2, respectively) of the Wechsler Memory Scale – Third Edition (WMS-III) [25]. Scores from the following CVLT-II subscales were utilized: a) total number of words recalled trials 1-5; b) short delay free recall; c) long delay free recall; and d) recognition. Scores from the following Logical Memory I and II subscales of WMS-III were utilized: a) LM1 Recall total score; b) LM2 Recall total score; and c) recognition. Other subscales were excluded from analysis to limit the number of potential dependent variables. Both tests have been used in clinical and research settings as neuropsychological measures of verbal memory functioning and have sound psychometric properties.

Design

This study employed a 3 X 4 between subjects, factorial design. The first factor was disease type and had three levels: 1) ETOH, 2) HCV and 3) OTHER. The second factor was disease severity as operationalized by the Model for End-Stage Liver Disease (MELD) score. The MELD score is the disease severity score used for listing patients for liver transplantation and is based on a mathematical model that uses laboratory values (serum total bilirubin,

creatinine, and international normalized ratio for prothrombin time; [26]. Disease severity was categorized based on the following MELD scores: less than 10 (mild), 11-15 (moderate), 16-20 (severe), and 21 and greater (very severe).

Data Analyses

Analyses were conducted on raw scores of each dependent variable. One-way analyses of variance (ANOVA) and chi-square analyses were employed to compare demographic and disease severity variables among the three disease etiologies. Multiple single sample t-tests were performed on each dependent measure for each disease etiology using each etiologic group's mean age and education as references to obtain published, normative (population) values. A Bonferroni correction was employed to account for multiple comparisons and to control for alpha inflation; significance differences were noted for t-scores with associated p-values less than 0.0083. Data were then analyzed using a 3 X 4 factorial, multivariate analysis of covariance (MANCOVA). The three covariates were age, depression and frontal lobe/executive functioning. Depression was operationalized as total score on the Center for Epidemiological Study's Depression Scales (CES-D; 27). Frontal lobe/executive functioning (verbal fluency) was operationalized as age- and education- adjusted standard score on the Controlled Oral Word Association test (COWA] [28, 29]. It was selected over other measures of frontal lobe functioning as it is a verbal measure, and thus taps the same sensory modality as the two dependent measures. These three variables were included as covariates as they have all been shown to negatively affect memory functioning [30]. Univariate analyses were employed to follow-up significant multivariate main effects, and a Bonferroni correction was employed to account for multiple comparisons and to control for alpha inflation.

SPSS Version 16.0 was the statistical software package used for all statistical analyses. Statistical significance was set at .05 for all analyses unless otherwise stated.

RESULTS

The sample consisted of primarily middle-aged (51.9 ± 9.6 years), right-handed (88%), married (73.6%) Caucasians (85.6%). Most had completed some post-secondary education, but individuals in the HCV group (12.4 ± 2.3 years) completed significantly fewer years of formal education compared to individuals in the OTHER group (14.0 ± 2.9 years), p=0.022. Furthermore, there were disproportionately more males in the ETOH group (72.5%) compared to individuals in the HCV (42.9%) and OTHER (41.9%) groups, p=0.007. There also were disproportionately more individuals currently in the workforce in the OTHER group (58.1%) compared to individuals in the ETOH (23.1%) and the HCV (31.0%) groups, p=.004 (see Table 1). The three etiologic groups did not significantly differ from one another across disease severity variables. Based on their MELD scores, the sample was comprised of individuals with moderate cirrhosis (see Table 2).

Table 1. Comparison of Demographic Variables by Liver Disease Etiology

Variable	ETOH	HCV	OTHER
N	40	42	43
Age (mean ± SD)	53.2 ± 7.1	52.8 ± 9.8	49.9 ± 11.3
Education (mean ± SD)	13.2 ±2,5	12.4 ± 2.3	14.0 ± 2.9
Right Handed (%)	87,2	90,5	88,7
Male (%)	72,5	42,9	41,9
Caucasian (%)	90	90,5	76,7
Married (%)	71,8	85,7	65,1
In the workforce (%)	23,1	31	58,1

Table 2. Comparison of Disease Severity Variables by Liver Disease Etiology (mean ± std dev)

Variable	ETOH	HCV	OTHER
N	40	42	43
Total Bilirubin mg/dL	3.2 ± 2.9	3.0 ± 2.5	4.5 ± 6.2
Creatinine mg/dL	1.3 ± 1.1	1.4 ± 1.7	1.2 ± 0.6
INR	1.6 ± 0.4	1.5 ± 0.4	1.4 ± 0.5
MELD	16.4 ± 5,6	15.5 ± 5,4	14.1 ± 6,7
Portal HTN (%)	46,9	46,3	25,6
History of Varices (%)	37,1	32,5	25
Ascites (%)	61,8	51,2	47,5
Edema (%)	21,2	17,9	17,9

Table 3. Pearson's Product Moment Correlation Coefficients among Dependent Variables

Variable	CVLT1-5	SDFR	LDFR	CVLT-RC	LM1	LM2	WMS-RC
CVLT1-5	1.000	.849*	.841*	.462*	.583*	.501*	.449*
SDFR		1.000	.813*	.496*	.541*	.497*	.431*
LDFR			1.000	.465*	.524*	.520*	.380*
CVLT-RC				1.000	.176**	.195**	.091^{ns}
LM1					1.000	.847*	.609*
LM2						1.000	.672*
WMS-RC							1.000

All correlational analyses were conducted on raw scores. CVLT1-5 = CVLT-II 1-5 total recall; SDFR = CVLT-II short delay free recall; LDFR = CVLT-II long delay free recall; CVLT-RC = CVLT-II recognition; LM1 = WMS-III Logical Memory I total recall; LM2 = WMS-III Logical Memory II total recall; WMS-RC = WMS-III Logical Memory Recognition. ** = significant at the p=.05 level; * = significant at the p=.01 level; ns = non-significant association.

Table 4. Descriptive Statistics of Selected Measures by Liver Disease Etiology

Variable	ETOH	HCV	OTHER
N	40	42	43
CVLT-II (mean ± SD)			
sdfr raw	7.6 ± 3.1	9.1 ± 3.1	9.3 ± 3.5
1-5 raw*	40.2 ±10.0	43.7 ± 10.4	47.1 ± 11.4
ldfr raw	7.7 ± 3.1	8.6 ± 3.9	9.6 ± 3.5
recognition	15.5 ± 2.0	13.8 ± 2.2	14.3 ± 2.1
WMS-III (mean ± SD)			
LM1 raw	33.6 ± 8.5	34.0 ± 11.3	36.4 ± 8.9
LM2 raw	19.2 ± 7.0	21.3 ± 7.8	22.3 ± 7.7
Recognition	24.2 ± 2.8	24.7 ± 3.2	25.1 ± 2.9
Endorsing memory	52,6	61,9	38,5
Problems (%)			
CES-D (mean ± SD)	15.7 ± 10.7	16.7 ± 10.7	13.4 ± 10.9
COWA (mean ± SD)	91.5 ± 16.6	95.6 ± 11.4	95.7 ± 13.4

Note. CVLT-II =California Verbal Learning Test – 2nd Edition, 1-5 raw = Trials 1-5 Total Score, sdfr raw = Short-Delay Free Recall raw score, ldfr raw = Long-Delay Free Recall raw score; WMS-III = Wechsler Memory Scale – 3rd Edition, LM1 = Logical Memory I raw score, LM2 = Logical Memory II raw score; CES-D = Centers for Epidemiological Studies – Depression Scale; COWA = Controlled Oral Word Association Test; * significant difference between ETOH and OTHER, $p < 0.05$.

Almost half of the sample (48.8%) reported subjective difficulties with memory functioning; these findings were independent of disease etiology, X^2 (2) = 4.49, p=0.106. Results from the multiple, single-sample t-tests indicated that individuals in the ETOH group performed significantly worse than age and education matched population norms on the CVLT-II short delay free recall (Mean = 7.6 vs. μ = 9.0), CVLT-II long delay free recall (Mean = 7.7 vs. μ = 9.0), and WMS-III LM1 Recall total score (Mean = 33.6 vs. μ = 39.5), p<0.0083. Individuals in the HCV group performed significantly worse than age and education matched population norms on the CVLT-II 1-5 raw total score (Mean = 43.7 vs. μ = 50.0), CVLT-II short delay free recall (Mean = 9.1 vs. μ = 11.0), CVLT-II long delay free recall (Mean = 8.6 vs. μ = 11.5), CVLT-II recognition (Mean = 13.8 vs. μ = 15.0), and WMS-III LM1 Recall total score (Mean = 34.0 vs. μ = 39.5), p<0.0083. Individuals in the OTHER group performed significantly worse than age and education matched population norms on the CVLT-II short delay free recall (Mean = 9.3 vs. μ = 11.0) and CVLT-II long delay free recall (Mean = 9.6 vs. μ = 11.5), p<0.0083.

Evaluation of the variance-covariance structure of the dependent variables revealed a high degree of correlation among variables ($0.198 < r < .849$, $p < 0.05$) (see Table 3). Consequently, the number of dependent variables for the multivariable analyses was reduced to: CVLT-II raw 1-5, CVLT-II long delay free recall, WMS-III LM1 and LM2. While these variables are also highly correlated ($0.520 < r < 0.841$), they were included because of their clinical significance.

Results from the original 3 X 4 MANCOVA revealed age and education to be non-contributory covariates; thus, they were removed from all further analyses. Results from the final model, which included the two independent variables (disease etiology and disease severity), the interaction term (disease etiology X disease severity) and a single covariate (COWA), revealed a significant multivariate main effect for disease etiology, F(8, 220) = 2.735, Pallai's Trace = .181, p=.007. Follow-up univariate analyses revealed a significant main effect for disease etiology on the CVLT-II 1-5 raw score, F(2, 112) = 3.42, p=.036. Post-hoc analyses revealed that individuals in the ETOH group (40.2 ± 10.0) performed significantly worse than individuals in the OTHER group (47.1 ± 11.4), p=.031. No other differences were significant (see Table 4).

DISCUSSION

This study is among the limited efforts specifically examining verbal memory functioning in individuals with cirrhosis presenting for consideration for liver transplantation. Perceived deficits in "memory" are common among individuals with cirrhosis, with approximately half (48.8%) of the sample endorsing difficulties with memory functioning within the year preceding their evaluation for possible liver transplantation. Objective measurements confirm the subjective complaints of memory impairments. Across neuropsychological measures of learning and memory, individuals with cirrhosis performed significantly worse than matched peers from population norm data. Additionally, individuals in all three diagnostic categories performed significantly worse than matched peers on the immediate and delayed recall of information presented in list form (i.e., CVLT-II short and long delay free recall). Furthermore, individuals with alcohol- and HCV-induced cirrhosis evinced impaired performance on the immediate recall of information presented in context (i.e., WMS-III LM1). Individuals with non-alcohol, non-HCV induced liver disease etiologies did not evince such deficits. Finally, individuals with HCV-induced cirrhosis also performed significantly worse than age- and gender-matched controls on a measure of learning across multiple presentations of the same material (CVLT-II 1-5 total raw score) as well as a measure of recognition (CVLT-II Recognition). As there have only been a limited number of published articles to date assessing the impact of HCV on cognitive functioning in general, these findings extend our current understanding of this emerging field [19, 31-34].

Notable differences in verbal memory functioning were also observed among the ESLD etiologies. Despite equivalent disease severity, individuals with alcohol-induced liver disease evinced poorer verbal learning and memory than individuals with non-alcohol, non-HCV-induced cirrhosis etiologies. Sustained periods of excessive alcohol consumption appear to result in greater verbal memory impairment than hepatic insufficiency alone, which is not surprising as the negative impact of alcohol on memory functioning is well documented and widely accepted [22, 35]. However, despite being adequately powered, this study failed to demonstrate a statistically significant difference between individuals with HCV-induced liver disease and individuals with non-alcohol, non-HCV cirrhosis etiologies, suggesting that the virus does not have a significant detrimental impact on memory functioning above and beyond the effects of hepatic insufficiency alone.

Functional differences among cirrhosis etiologies are suggestive of structural differences in the mechanism of action of the differing etiologies. It is well established that excessive alcohol consumption affects cognitive processes associated with cortical (e.g., frontal lobes) as well as subcortical (e.g., basal ganglia)

structures [36, 37]. On the other hand, studies utilizing *in vivo* proton magnetic resonance spectroscopy have revealed selective cerebral metabolite abnormalities in the basal ganglia and white matter in HCV-infected individuals, suggesting only subcortical involvement [31, 38]. However, to the authors' best knowledge, no studies have specifically examined the neurophysiological effects of non-alcohol and non-HCV related liver disease. Based on the findings from this study, indicating similar functioning in verbal learning among HCV-infected individuals and individuals with other disease etiologies, it appears that liver disease alone negatively affects subcortical structures without the impact on cortical structures that is seen in substance abuse.

Notable strengths of this study are a large, diverse sample and multiple measures of verbal memory functioning. Whereas past efforts have typically utilized small, heterogeneous samples, this study was conducted on fairly large sample (N=125) with three distinct liver disease etiologies. For example, McRea et al. [6] had a sample of twenty individuals with cirrhosis and twenty controls and found no memory dysfunction. With such a small sample size, statistical analyses were likely underpowered and non-significant findings are not entirely unexpected. Additionally, the inconsistencies in the literature regarding memory impairments among individuals with liver disease may be a consequence of disparate methods of measurement. Notably, deficits in memory function relative to normative values were more evident across subscales of the CVLT-II compared to subscales from the WMS-III. Significant differences also were observed among the three ESLD etiologies on a subscale from the CVLT-II, but no statistically significant differences were observed across subscales from the WMS-III. Thus, the results support previous findings that individuals with liver disease do not evince impairments on many measures of the Wechsler memory scales [4, 6] but do evince impairments on measures of learning and memory that employ list learning [19].

Although findings from this study provide evidence of a statistical difference among individuals with ESLD relative to published norms and among ESLD etiologies, these findings may not be clinically meaningful in and of themselves. Across measures of learning and memory and disease etiologies, individuals with ESLD perform 0.5 to 1 standard deviations below their peers; however, these performances still fall within the average to low average range of functioning overall. In light of the frequency with which individuals self-report memory impairments and while not necessarily indicative of clinically meaningful neuropsychological impairment alone, recognizable changes in cognitive functioning have the potential to contribute to psychological distress, and SHE has been shown to negatively affect overall quality of life [39-41].

A better understanding of the verbal memory dysfunction evident among individuals with ESLD has the potential to improve patient care. Individuals living with chronic conditions are becoming increasingly responsible for the day-to-day management of their disease. Medical staff typically provides information necessary to manage a chronic condition verbally. Most medical interventions – pharmacological as well as behavioral – have been shown to be more beneficial than harmful when followed as prescribed, and noncompliance with prescribed regimens undermines the possible benefit achievable from these interventions [42-44]. Strict compliance with medical recommendations becomes especially important for individuals with ESLD who undergo transplantation. During the post-transplantation period, the ability to recall specific instructions and apply them as specified is imperative to survival, as even a slight fever may be an early indication of graft rejection. Strict adherence to medication (e.g., immunosuppressive regimens) as well as dietary and substance use restrictions is a requisite to successful transplantation outcomes.

While the current findings highlight the relative impairment of verbal memory functioning among individuals with ESLD compared to published norms, the design of this study did not employ a control group, and consequently, interpretation of these findings should take this limitation into account. Furthermore, disproportionately more males had alcohol-induced liver disease. This finding, however, is not entirely surprising as there are disproportionately more males in alcohol treatment programs, even among those programs that specifically target female populations [45-47]. Nonetheless, this is a limitation of this study, and results should be interpreted with caution. Of note, the design of the current study is not capable of adequately describing the nature of the deficits in verbal memory. Future research should examine the degree to which impairments in verbal memory functioning are a result of deficiencies in encoding, consolidating and/or retrieving newly learned information. Finally, it is noteworthy that individuals with HCV typically have significant alcohol and drug histories [48,49], and individuals with HCV who drink alcohol in excess have more severe histological injury, faster disease progression, and a greater incidence of hepatocellular carcinoma and cirrhosis [50]. However, the current analyses were limited to individuals with HCV but without concomitant histories of alcohol use. Therefore, all conclusions regarding the effect of HCV on verbal memory functioning should be limited to this

select population. Future research should examine the additive effects of alcohol and HCV on verbal memory functioning

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