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ORIGINAL ARTICLE

Effect of Post-Traumatic Stress Disorder on Cognitive Function and Covert Hepatic Encephalopathy Diagnosis in Cirrhotic Veterans

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Abstract

Background In veterans, post-traumatic stress disorder (PTSD) is often associated with substance abuse, which in turn can lead to cirrhosis. Cirrhotic patients are prone to cognitive impairment, which is typically due to covert hepatic encephalopathy (CHE), but can also be affected by PTSD. The aim was to define the impact of PTSD on cognitive performance and the diagnosis of CHE in cirrhotic patients.

Methods Outpatient veterans with cirrhosis underwent two separate modalities for CHE cognitive testing [Psychometric Hepatic Encephalopathy Scale (PHES) and Inhibitory Control Test (ICT)]. ICT tests for inhibitory control and response inhibition, while PHES tests for attention and psychomotor speed. Comparisons were made between patients with/without PTSD. Multivariable logistic regression with CHE on PHES and CHE on ICT as dependent variables including prior OHE, demographics, PTSD and psychotropic medications was performed.

Results Of 402 patients with cirrhosis, 88 had evidence of PTSD. Fifty-five of these were on psychoactive medications, 15 were undergoing psychotherapy, while no specific PTSD-related therapy was found in 28 patients. Cirrhotic patients with/without PTSD were statistically similar on demographics and cirrhosis severity, but cirrhotic subjects with PTSD had a higher frequency of alcoholic cirrhosis etiology and psychotropic drug use. PTSD cirrhosis had higher ICT lure and switching errors (NCT-B response), but on regression, there was no significant impact of PTSD on CHE diagnosis using either the ICT or PHES.

Conclusions Veterans with cirrhosis and PTSD have a higher frequency of psychotropic drug use and alcoholic cirrhosis etiology. CHE diagnosis using PHES or ICT is not affected by concomitant PTSD.

Keywords Psychometric hepatic encephalopathy score · Inhibitory control test · Psychotropic medications · Age · Education

Introduction

Cirrhotic patients with covert hepatic encephalopathy (CHE) are more likely to have cognitive impairment, report poorer health-related quality of life, and have more difficulty with daily functioning and driving [1, 5, 14]. CHE has been diagnosed in a large proportion of cirrhotic patients, and it has prognostic value [5]. The primary areas of dysfunction in CHE include psychomotor, executive, working memory, and attention, whereas short- and long-term memory remains predominantly intact [3, 13, 17]. Tests used for CHE typically are sensitive but are not necessarily specific. This lack of test specificity may reflect the fact that cognitive impairment in these individuals may be multifactorial in nature, with comorbid mental health conditions potentially having

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a role. Further examination of mental health conditions and cognitive impairment in cirrhotic patients with CHE is important due to the recent advances in diagnostic measures and the clinical impact on health and functioning.

Specifically, post-traumatic stress disorder (PTSD), which can affect cognitive functioning, has not been examined as a factor for cognitive impairment in cirrhotic patients. PTSD is one of the primary concerns of veterans returning from combat, with estimates of the prevalence being 18–19%, and poses a significant health concern for veterans due to its comorbidity with numerous medical conditions [7, 11, 15]. Wrocklage et al. [18] detailed the neuropsychological profile of veterans with PTSD. Results mirrored prior studies [8] and showed veterans with PTSD to have significant dysfunction in information processing, executive function, attention, and working memory even after controlling for depression, prior history of head injuries, and substance use. These areas of neuropsychological impairment directly show considerable overlap with those evident in cirrhotic patients. This presents a challenge for the clinician to disentangle the relative contribution of PTSD to the neurobehavioral profile associated with cirrhosis.

The relative contribution of PTSD in abnormal performance of tests used to diagnose CHE is relevant for the veteran population. Using a battery of tests that emphasize both subcortical and frontal region processing may allow us to better understand the overlap in terms of the cognitive "fingerprint," as well as the cognitive differences in the background of cirrhosis. Our aim was to determine the impact of PTSD on the overall cognitive performance in cirrhotic veterans using strategies that are currently used to define CHE in these patients.

Methods

Patients with cirrhosis for this study were recruited from the McGuire VA Medical Center to participate in the current study from July 2008 to January 2016. Cirrhosis was diagnosed via biopsy, radiologic evidence of the disease, endoscopic evidence of varices in a patient with chronic liver disease, or those with frank decompensation (history of variceal bleeding, ascites, or prior Overt Hepatic Encephalopathy). Patients with a history of overt hepatic encephalopathy (OHE) were included in the study if they were sufficiently controlled on medications (lactulose and/or rifaximin) when enrolled. Subjects were determined as able to provide informed consent by scoring ≥ 25 on the mini mental status examination and having dementia ruled out via interview and family history. Subjects were excluded if they were unable to provide consent, had abused alcohol or illicit substances in the past 3 months, or were on psychoactive medications apart from antidepressants, similar to prior studies [2]. The McGuire VA Institutional Review Board approved this study.

Upon receiving informed consent, information was collected from their medical record related to their liver function, cirrhosis details (e.g., etiology, duration, complications), adherence to current medications, and the presence and status of a PTSD diagnosis within 12 months prior to participating in the study. The subjects then underwent two cognitive strategies to assess neuropsychological compromise associated with cirrhosis: the Psychometric Hepatic Encephalopathy Scale (PHES) and Inhibitory Control Test (ICT).

Psychometric Hepatic Encephalopathy Scale (PHES) This scale is derived from a composite of five tests. These tests include: (1) a timed task requiring the subject to connect numbered dots (NCT-A), (2) a timed task where the subject must alternate connecting numbered and lettered dots (NCT-B), (3) a digit symbol test (DST) involving the pairing of number with corresponding symbol within 120 s, (4) a motor speed task requiring subjects to dot individual circles (serial dotting test, SDT), and (5) a line-tracing task where the subject completes a maze without touching the sides, which is scored by adding errors + time as the outcome (line-tracing test, LTT). For the USA, scores below − 4 are deemed to be abnormal [2]. The PHES has been found to be a reliable and valid measure of CHE and has been validated for use in cirrhosis in the USA [2, 12, 16].

Inhibitory Control Test (ICT) In this computerized test of response inhibition, subjects respond to two different stimuli, lures, and targets, presented on the screen. Subjects are instructed to inhibit their responses to lures and only respond when presented with targets. The test performance was used in context of norms [2, 4].

PTSD Diagnosis A PTSD diagnosis was assigned if the subject had a recorded PTSD diagnosis by a mental health provider in their medical record. Information was also collected in medical records about whether the subjects were prescribed psychotropic medications, or if they were attending psychotherapy within 1 month of participating in this study.

Statistical Analysis

Descriptive statistics were performed for each of the variables. Comparisons were made between patients with and without PTSD. Continuous variables were analyzed using ANOVAs, while categorical variables were analyzed with Chi-square. Separate multivariable logistic regression was performed using abnormal performance on PHES and abnormal performance on ICT as dependent variables. Variables included in a backward logistic regression model included prior OHE, use of rifaximin (signifying worse

OHE), demographics, alcoholic etiology of cirrhosis, diagnosis of PTSD, and use of psychotropic medications.

Results

In total, 402 (389 men) subjects were included in the present study for the analyses. The mean age was 58 years old, and there was a mean of 13 years of education. Of these 402 patients with cirrhosis, 88 (21.9% of total sample) had evidence of PTSD (Table 1). Of these 88, 55 (62.5%) were on psychotropic medications, 15 (17%) were undergoing psychotherapy, while no specific PTSD-related therapy (medication or psychotherapy) was found in 28 (31%) of patients. Patients with/without PTSD were statistically similar on demographics and cirrhosis severity. All patients on HE therapy were adherent on it confirmed via direct questioning and analysis of their medical records.

Psychotropic medication use was found in 125 subjects. Primarily, these medications were antidepressants (SSRIs $n = 67$, SNRIs = 34) followed by benzodiazepines $n = 12$, aripiprazole $n = 5$, buspirone $n = 2$, quetiapine $n = 2$, hydroxyzine pamoate $n = 2$, and lithium $n = 1$.

Table 1 Comparison between patients with and without PTSD

	Cirrhosis without PTSD ($n = 314$)	Cirrhosis with PTSD ($n = 88$)
Age (years)	58.2 ± 6.6	58.8 ± 7.4
Education (years)	13.5 ± 2.3	13.1 ± 2.1
Child–Turcotte–Pugh Score	8.4 ± 3.5	8.7 ± 4.1
MELD score	12.4 ± 4.9	11.9 ± 4.2
HCV etiology of cirrhosis	159 (51%)	41 (46%)
Alcoholic etiology of cirrhosis	77 (17%)	35* (40%)
Prior OHE	105 (33%)	30 (34%)
On lactulose	99 (31.5%)	31 (35.2%)
On rifaximin	52 (16.6%)	18 (20.5%)
Psychotropic meds	70 (22.3%)	55* (62.5%)
ICT lures (no. responded to)	14.23 ± 9.1	16.8 ± 9.6*
ICT targets (% correct)	91.2 ± 12.4	90.8 ± 12.0
Number connection-A (s)	46.2 ± 24.3	51.2 ± 26.0
Number connection-B (s)	134.8 ± 89.0	161.0 ± 113.0*
Digit symbol (s)	45.4 ± 14.2	43.9 ± 15.0
Line-tracing errors (number)	33.0 ± 30.0	34.2 ± 26.1
Line-tracing time (s)	118.1 ± 57.7	117.6 ± 50.8
Serial dotting (s)	86.3 ± 40.2	90.8 ± 50.7
PHES total score	− 5.0 ± 4.4	− 5.9 ± 4.9
CHE by PHES	168 (53.5%)	51 (57.9%)
CHE by ICT	204 (64.9%)	65 (73.9%)

CHE covert hepatic encephalopathy, *PHES* psychometric hepatic encephalopathy score, *ICT* inhibitory control test, *OHE* overt hepatic encephalopathy, *HCV* hepatitis C virus

*$p < 0.05$, data presented as mean ± SD unless mentioned

Although lures were statistically higher in PTSD subjects, there was no significant difference in the proportion of subjects diagnosed with CHE using the ICT in the PTSD group compared to the no-PTSD group. Similarly for the PHES individual tests, there was a higher NCT-B score, and a trend toward a worse total score in PTSD subjects, but no difference in the overall PHE-based CHE prevalence associated with PTSD diagnostic classification. When we compared the 28 PTSD patients who were not on therapy to the rest, CHE rates by PHES (16 of 28 vs 35 of 60, $p = 0.89$) and ICT (22 of 28 vs 43 of 60, $p = 0.64$) were statistically similar between groups.

Using the multivariable logistic regression that included independent variables HCV etiology, alcoholic etiology, age, MELD score, education, prior OHE, rifaximin use, PTSD, and psychotropic medications with PHES CHE as the dependent variable, the significant predictors were age (OR 1.09, 95% CI 1.05–1.13 $p < 0.001$) and prior OHE (OR 3.49, 95% CI 2.13–5.72, $p < 0.0001$). Using the same variables but with ICT CHE as the dependent variable, the significant predictors were age (OR 1.04, 95% CI 1.01–1.06, $p = 0.04$) and education (OR 0.90, 95% CI 0.82–0.99, $p = 0.03$). Neither PTSD diagnostic classification nor the use of psychotropic medications was predictive of CHE in the final models using either cognitive assessment methodologies (e.g., PHES and ICT).

Discussion

The current results find that in the complicated clinical background of cirrhosis and cognitive dysfunction, two important CHE diagnostic strategies (i.e., PHES and ICT) are unaffected by the presence of cognitive change associated with PTSD. Patients with PTSD had a statistically similar liver disease severity, including prevalence of OHE, compared to those without PTSD. While cirrhotic patients with PTSD had a higher proportion of alcoholic etiology, greater use of psychotropic medications, and a higher response rate to ICT lures (reflecting response disinhibition), CHE diagnostic prevalence was statistically similar across the two cognitive assessment methodologies.

These results indicate that subjects with a diagnosis of PTSD had poorer performance on the ICT lures than those without PTSD. The most likely reason for these findings is that the ICT is more sensitive to symptoms associated with PTSD, specifically an impaired inhibitory response, which has been found to be particularly poor in this population due to heightened arousal [9, 10, 18]. This arousal leads to increased impulsivity, and thus, patients will perform worse on tasks requiring the ability to quickly inhibit a response. Nevertheless, the current findings demonstrate both the PHES and ICT to be sensitive and specific as a CHE

diagnostic method. Indeed, the fact that the ICT and PHES demonstrated consistent prevalence rates despite a higher proportion of an alcohol cirrhotic etiology in the PTSD subjects and the equivalent rate of CHE despite PTSD therapy within the PTSD group provides additional validity support for the use of these cognitive diagnostic methods. Interestingly, in comparison with the ICT, the PHES—which has previously been shown to have strong sensitivity and specificity and is considered the gold standard for diagnosing CHE—did not result in greater CHE diagnostic specificity, although the NCT-B was significantly higher in PTSD subjects.

Due to the high prevalence of cirrhosis and subsequent manifestation of CHE in the veteran population and their unique characteristics compared to civilians, understanding the effects of PTSD on CHE diagnostic methods is an important undertaking. The present findings are clinically relevant for informing providers which task to use when diagnosing CHE in this population fraught with several cognitive insults. Indeed, our patient population reflects what is currently seen in VA centers nationwide and is applicable to a broad swathe of these individuals. The study findings support the use of both ICT and PHES as methods for diagnosing CHE while at the same time minimizing potential neurobehavioral confounds of PTSD. The PHES in comparison with the ICT, in the USA, requires psychological expertise for ordering, administering, and interpreting. This limits its use in clinical settings. Given these constraints, the ICT can be used as a suitable diagnostic alternative.

The study is limited by the predominant male population, which limits its generalizability to female and civilian cirrhotic patients. Also, a limitation of the study is that PTSD diagnoses were obtained via a medical chart review versus during the course of data collection. While it can be assumed the majority of medical charts reflect accurate diagnoses made during clinical encounters, there remains the possibility that a diagnosis of PTSD was charted in error. With that said, the fact that ICT (i.e., frequency of Lures) and PHES performance (i.e., NCT-B) significantly differed based on medical chart recorded PTSD diagnosis provides support for the VA Hospital psychiatric diagnostic methodology. An additional limitation is the absence of information about depressive symptoms, which could have a significant impact on the cognitive function, and subsequently the neuropsychological performance, of participants in the study. Although we determined the psychotropic medications such as SSRIs as a marker of depressive symptoms, future studies should examine a wider range of psychological functioning in relation to CHE diagnosis. The psychotropic medications can also confound the ultimate impact of PTSD; however, the pattern with the majority of antidepressants is similar to prior studies and did not significantly impact the ultimate CHE diagnosis on multivariable analysis [6]. Also, while PTSD is a chronic and persisting condition, it cannot be assumed that subjects with an identified PTSD diagnosis were exhibiting active symptomology at the time of assessment when the ICT and PHES were administered.

We conclude that PTSD can influence individual components of cognitive testing strategies in cirrhotic Veterans. However, both ICT- and PHES-associated CHE classifications are not significantly affected by the diagnosis of PTSD. Therefore, the use of either of these strategies can be used to define CHE in cirrhotic Veterans regardless of PTSD.

Compliance with Ethical Standards

Conflict of interest No conflicts of interest exist for any author. This study was partly supported by VA Merit Review I0CX001076 to JSB.

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