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Cognitive Reserve is a Determinant of Health-Related Quality of Life in Patients with Cirrhosis, Independent of Covert Hepatic Encephalopathy and MELD Score

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Abstract

Background & Aims—Covert hepatic encephalopathy (CHE) is associated with cognitive dysfunction, which affects daily function and health-related quality of life (HRQOL) in patients with cirrhosis. The effects of CHE and liver disease are determined by cognitive reserve—the ability of the brain to cope with increasing damage while continuing to function—and are assessed by composite intelligence quotient (IQ) scores. We examined cognitive reserve as a determinant of HRQOL in patients with cirrhosis.

Methods—We performed a prospective study of 118 outpatients with cirrhosis without overt HE (age, 56 years). We studied cognition using the standard paper-pencil battery; patients with below-normal results from more than 2 tests were considered to have CHE. We also assessed HRQOL (using the sickness impact profile, sickness impact profile (SIP), psychosocial and physical scores (a high score indicates reduced HRQOL), model for end-stage liver disease (MELD) scores, and

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cognitive reserve (using the Barona Index, a validated IQ analysis, based on age, race, education, residence area, and occupation). Cognitive reserve was divided into average and high groups (below or above 109), and MELD and SIP scores were compared. We performed regression analyses, using total SIP score and psychosocial and physical dimensions as outcomes, with cognitive reserve, CHE, and MELD score as predictors.

Results—Study participants had average MELD scores of 9, and 14 years of education; 81% were white, 63% were urban residents, their mean IQ was 108±8, and 54% had average cognitive reserve (the remaining 46% had high reserves). CHE was diagnosed in 49% of patients. Cognitive reserve was lower in patients with than CHE (109) than without (105, *P*=.02). Cognitive reserve correlated with total SIP and psychosocial score (both r= −0.4; *P*<.001) and physical score (r= −0.3; *P*=.01), but not MELD score (*P*=.8). Patients with high cognitive reserve had better HRQOL, despite similar MELD scores. In regression analyses, cognitive reserve was a significant predictor of total SIP (*P*<.001), psychosocial (*P*<.001), and physical scores (*P*<.03), independent of CHE, MELD, or psychiatric disorders.

Conclusion—A higher cognitive reserve is associated with better HRQOL in patients with cirrhosis, despite similar disease severity and prevalence. This indicates that those with good cognitive reserve are better able to withstand the demands of cirrhosis progression and CHE, leading to a better QOL. Patients with lower cognitive reserve may need more dedicated and earlier measures to improve HRQOL. Cognitive reserve should be considered when interpreting HRQOL and cognitive tests to evaluate patients with cirrhosis.

Keywords

minimal hepatic encephalopathy; prognostic factor; coping; nervous system

INTRODUCTION

Hepatic encephalopathy (HE) continues to pose a major burden on patients, caregivers, and society. [1] It is described as a spectrum of neurocognitive changes in cirrhosis (SONIC) in which covert HE, which cannot be readily diagnosed clinically, occurs in up to 60% of tested patients.[2] CHE presents a burden to both patient and family as it has been shown to be associated with deficits in driving skills, daily executive decision making, and more importantly, health-related quality of life (HRQOL).[3–6] HRQOL is associated with CHE and can strongly impact survival and socio-economic status.[5, 7] Since HRQOL is a personal assessment of issues facing the patient, the results are affected by several factors such as age, gender, education, socio-economic status, and cognitive reserve. The construct cognitive reserve is thought to reflect the brain's ability to maintain cognitive function in the setting of neurocognitive insult or underlying brain disease. Cognitive reserve has been shown to modulate the personal impact of disease progression in traumatic brain injury (TBI), dementia, and multiple sclerosis (MS).[8–11] However the impact of cognitive reserve on HRQOL remains underappreciated in cirrhosis.

Our aim was to evaluate the impact of cognitive reserve on personal assessment of HRQOL in the context of liver disease severity and CHE diagnosis. We hypothesized that patients

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with higher cognitive reserve would have a better HRQOL than those with normal cognitive reserve despite similar cirrhosis severity and cognitive dysfunction.

METHODS

From 2008 to 2012, we prospectively enrolled outpatients with cirrhosis from liver clinics at VCU Medical Center after written, informed consent. Cirrhosis was diagnosed via biopsy, radiological or endoscopic evidence of varices, or laboratory results in patients with chronic liver disease. Those excluded were: patients unable to understand English, patients with a history or alcohol or illicit drug use in the previous six months, those on any psychoactive medications except chronic antidepressants/anxiety or chronic opioids, those with current or prior episodes of overt HE or on HE treatment.

At the initial visit, we calculated the MELD score and performed a battery of standard cognitive tests to diagnose CHE: number connection test (NCT) A and B, the digit symbol test (DST), and the block design test (BDT). An impairment of two or more tests compared to healthy controls, was considered CHE.[12] We also administered the validated HRQOL Sickness Impact Profile (SIP) questionnaire which consists of 136 items divided into 12 groups: sleep and rest, work, eating, recreations and pastimes, home management, mobility, ambulation, social interaction, body care and movement, emotional behavior, communication, and alertness.[13] Patients were asked to answer only those questions pertinent to their health from the past 24 hours. The SIP contains a total score with physical and psychosocial domains. The higher the SIP score, the worse the HRQOL. Cognitive reserve was calculated using the Barona Index, which consists of age, sex, race, formal years of education, residence type (urban or rural), region of residence (locations within the USA), and their occupation at time of testing (divided into six types based on labor type).[14] The Barona index is an optimal method for testing pre-morbid intelligence that tracks subject cognitive performance. [15] Occupations can be broadly categorized as blue collar, white collar and a category comprising of retired/homemaker and disabled persons. The Barona IQ is divided into the verbal IQ (VIQ), performance IQ (PIQ), and the full scale IQ (FSIQ); we used the FSIQ as our measure for cognitive reserve. High cognitive reserve is defined as FSIQ ≥ 109 while lower than 109 is considered average cognitive reserve.[16]

Their demographics, liver disease severity, CHE diagnosis rates, psychiatric diagnoses, and SIP scores were compared between the two groups, with a significant difference of a p value being less than 0.05. Multivariable regression analysis was then performed using SIP total, physical and psychosocial domains, as dependant variables. This protocol was approved by the IRB at VCU Medical Center.

RESULTS

One hundred and eighteen patients with cirrhosis were included in the study. Fifty three or 45% were male with a mean age of fifty five years. The FSIQ was 107.6±8.0 with a median of 107.4 (range 85.17 to 120). Using the cut-off of 109 on the FSIQ, 64 (54%) had an average cognitive reserve, while 54 (46%) had a high cognitive reserve. Sixty patients (49.2%) patients had CHE. We found a diagnosis of depression in 32 (27.1%) patients which

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was treated with SSRIs, anxiety in 8 (6.7%) patients treated with SSRIs and use of chronic opioids for chronic pain in 34 (29%) patients; all chronic pain patients also had depression.

The cognitive reserve was lower in CHE patients compared to those without CHE (109 vs 105, p=0.02). We found no statistical difference in age with a significantly higher percentage of men in the average cognitive reserve group compared to the high cognitive reserve group. No difference in cognitive reserve in those with/without chronic pain, depression or anxiety was seen. However, the average cognitive reserve group did have significantly higher total, physical, and psychosocial SIP scores, indicating a worse HRQOL in those with lower cognitive reserve (Table 1).

Patients with depression had a worse HRQOL on total SIP (16.6±13.3 vs. 8.2±10.6, p=0.002), psychosocial (17.5±16.7 vs. 8.2±14.2, p=0.008) and physical SIP domains (10.0±10.6 vs. 4.5±6.0, p=0.005). Patients with anxiety had a worse total SIP (21.6±11.0 vs. 9.4±11.5, p=0.007) and psychosocial domain (30.3±16.3 vs. 8.9±14.1, p=0.002) but not physical SIP results (9.3±7.6 vs. 5.2±8.1, p=0.14). Chronic pain did not significantly impact SIP results. There was no significant correlation between MELD score with FSIQ, VIQ or PIQ (all p>0.84) and similarly MELD score was not significantly different between those with and without CHE (9.4 vs 8.5, p=0.08). There was a significant correlation between FSIQ and total SIP (r=−0.43, p<0.0001), psychosocial domain (r=−0.41, p<0.0001) and physical domain (−0.3, p<0.0001). Similarly VIQ was correlated with total SIP (r=−0.4, p<0.0001), psychosocial domain (r=−0.41, p<0.0001) and physical domain (r=−0.3, p<0.0001). PIQ was also related significantly to total SIP (r=−0.44, p<0.0001), psychosocial domain (−0.4, p<0.0001) and physical domain (r=−0.3, p<0.0001).

Univariate analysis was performed with age, gender, cognitive reserve, etiology of cirrhosis (HCV vs. no HCV), MELD score, depression, anxiety, chronic pain and CHE. Of the mentioned variables, cognitive reserve, depression, anxiety and CHE were significant on univariate analysis and were included in the multi-variable analysis with dependent variables of total, physical, and psychosocial SIP. Cognitive reserve (p<0.0001) was significantly predictive of total SIP independent of depression (0.001), anxiety (p=0.053) and CHE (p=0.04). Similarly the psychosocial domain of SIP was predicted by cognitive reserve (p<0.001), depression (p=0.014), anxiety (0.01) and CHE (p=0.05). The physical domain was predicted by cognitive reserve (p=0.04), depression (p=0.004), CHE (p=0.03) and MELD score (p=0.09).

DISCUSSION

Cognitive reserve remains underappreciated in patients with cirrhosis. Our study shows that despite having similar liver disease severity and rate of CHE, cirrhotics with higher cognitive reserve have a better HRQOL than those with average cognitive reserve.

Since recent advances have increased the life expectancy of patients with cirrhosis, their psychosocial functioning as well as factors that encourage patients to continue being productive members of society has gained importance. Patient-reported HRQOL is a critical determinant of this functionality and should feature in the clinicians' decisions for therapy

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and counseling. [17] In some studies, HRQOL itself is associated with poor outcomes, including mortality.[7, 18] We found that similar to prior studies, that depression, anxiety and chronic pain affected HRQOL.[19] However they did not impact cognitive reserve assessment. Therefore clinicians should be aware of factors other than the disease process that impacts the HRQOL as potential determinants affecting disease progression, adherence, and socio-economic status.

The concept of cognitive reserve may be essential to understanding the individualized differences in daily functioning as a result of cirrhosis. Therefore, patients with lower education and relatively unskilled occupation history may feel the impact of the disease much more readily at the same MELD score compared to those with better educational, socio-economic and occupational histories. This increases the impact of this condition given that the socio-economic status is already impacted in these blue-collar workers.[6, 20, 21] This concept is also important because it suggests that those patients with limited cognitive reserve are like to require greater multidisciplinary treatment intervention.[22] For example, these patients may require earlier intervention and aggressive cognitive rehabilitation therapy to prevent further possible decline in daily function represented by the HRQOL.

Our findings are even more striking considering that we excluded patients with prior overt HE, who tend to have worse overall HRQOL that our current study population.[23] This exclusion was to reduce the confounding of the decreased insight that accompanies overt HE that could have impacted the patient-reported HRQOL assessment.[24] Cognitive reserve was also not influenced by the MELD score and was not impacted by abnormal psychometric tests used to diagnose CHE in this population, demonstrating this additional layer of complexity that is needed to interpret HRQOL and daily function results in cirrhotic patients.

In both cross sectional and longitudinal studies, cognitive reserve in several neurologic disorders has been shown to impact disease-associated HRQOL. In multiple sclerosis (MS) higher reserve scores were associated with better HRQOL, lower levels of disability, and higher feelings of functional health and overall well-being.[25] MS-associated disease progression was more strongly linked to cognitive decline in patients with lower intellectual enrichment and that a higher cognitive reserve protected against declines in cognitive efficiency and memory.[10] Similarly higher cognitive reserve was associated with lower incidence of dementia and complex leisure activities with physical, mental, and social stimulation have the most effect on attenuating dementia risk. [8, 26] Our study extends these findings into the realm of cirrhotic patients in whom the HRQOL is the composite of the liver disease severity and the behaviors that led to the cirrhosis (drug use or alcohol) and concomitant psychiatric issues, against the background of educational and occupational attainment. However the impact of cognitive reserve and CHE on HRQOL was significantly more compared to the etiology and severity of cirrhosis. This is likely due to the exclusion of overt HE patients, the relatively narrow range of MELD scores and abstinence from alcohol that was required for inclusion.

Although the Barona IQ determination involved factors such as education, occupation, and residence area, it does not take into account a person’s cognitive leisure activities, which

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may serve as another means of intellectual enrichment. But despite this, we found a strong relationship between cognitive reserve (as measured by the Barona index) and HRQOL in CHE. As shown in prior conditions, activities that involve stimulating, multiple cognitive domains, such as reading, complex game playing and social interactions could also potentially be used to improve HRQOL through cognitive reserve enhancement in cirrhotics.[8, 9, 25–29]; but further dedicated studies are required to assess this potential.

Our study is limited by its cross-sectional nature however even this snapshot provides insight into factors impacting the HRQOL. Longitudinal studies of the impact of cognitive reserve and HRQOL on outcomes such as overt HE development are warranted. This would help clarify whether different levels of cognitive reserve impact illness course. Sickness Impact Profile only inquires about the last 24 hours and is non-specific for cirrhosis; it is possible that focused questionnaires that assess function over longer periods of time could have differing results. [30] However, it is likely that the recall of functioning over the past 24 hours is more accurate compared to that of a longer duration.

In conclusion, our study showed that despite controlling for liver disease severity and rates of covert HE, cirrhotics with lower cognitive reserve have a worse HRQOL. Patients who are able to cognitively stimulate themselves and engage in complex tasks throughout life, such as via a challenging occupation and/or pursuing advanced education may enjoy a certain degree of protection from lifestyle disruption (represented in this study by HRQOL) despite worsening liver disease and cognitive function. Ultimately, clinicians could use this information to adapt their message to their cirrhotic patients. Targeting treatment in cirrhotics with lower cognitive reserve could potentially improve their daily functioning and enhance the HRQOL.

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Abbreviations List

HE	hepatic encephalopathy
CHE	covert hepatic encephalopathy
SONIC	spectrum of neurocognitive changes in cirrhosis
HRQOL	health-related quality of life
TBI	traumatic brain injury
MS	multiple sclerosis
NCT	number connection test
DST	digit symbol test
BDT	block design test

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SIP	sickness impact profile
VIQ	verbal intelligence quotient
PIQ	performance intelligence quotient
FSIQ	full scale intelligence quotient

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TABLE 1

Baseline Demographics and Cognitive Testing

	Average Cognitive reserve (n = 64)	High Cognitive reserve (n = 54)	P value
Age	55.3 ± 8.0	56.0 ± 5.4	0.58
Gender (% men)	57%	33%	0.003
Race (Caucasian/African-American /Hispanic)	44/19/1	53/0/1	0.03
Employment (blue collar/white collar/others)	17/19/28	2/46/6	<0.0001
Years of education	12.9 ± 1.7	15.5 ± 2.2	< 0.0001
Etiology of cirrhosis(HCV/ Alcohol/Alcohol+HCV/NASH/others)	32/5/1/15/11	21/3/1/19/9	0.45
Depression on treatment	19 (29%)	13 (24%)	0.49
Anxiety on treatment	5 (8%)	3 (5%)	0.72
Chronic pain on narcotics	17 (27%)	17 (31%)	0.56
MELD score	8.9 ± 3.2	9.0 ± 2.8	0.92
Covert HE			
Percent with Covert HE	50%	55%	0.62
Impaired Number connection-A	22 (35%)	14 (26%)	0.32
Impaired Number connection-B	18 (28%)	11 (20%)	0.33
Impaired Digit Symbol	40 (74%)	33 (61%)	0.88
Impaired Block Design	32 (50%)	16 (30%)	0.03
Health-related Quality of Life			
Total SIP score	12.5 ± 13.0	6.6 ± 7.8	0.003
Psychosocial SIP score	6.9 ± 9.4	3.8 ± 5.7	0.03
Physical SIP Score	12.2 ± 15.3	6.2 ± 9.7	0.01
Individual SIP domains			
Sleep and rest	24.7±27.3	11.7±16.1	0.002
Eating	3.5±6.1	1.9±3.8	0.10
Work	24.9±30.5	11.6±20.5	0.006
Home management	12.2±14.5	8.3±11.9	0.12
Recreation and pastimes	15.4±13.5	13.5±17.9	0.59
Ambulation	25.3±32.5	9.4±16.7	0.001
Mobility	7.5±11.4	3.5±7.8	0.03
Body care and movement	5.3±8.2	3.2±5.4	0.08
Social interaction	12.4±16.2	6.5±9.0	0.01
Alertness	7.7±10.8	6.2±8.2	0.37
Emotional behavior	11.5±16.2	6.8±11.8	0.07
Communication	9.8±17.2	2.0±5.5	0.001