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Factors That Affect Results of Psychometric Tests to Identify Patients With Minimal Hepatic Encephalopathy

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Keywords

Cirrhosis; Liver Disease; Alcohol; Diabetes

Introduction

Of the clinical complications of cirrhosis, hepatic encephalopathy (HE) is the most devastating. HE is a spectrum of reversible cognitive changes ranging from minimal HE (MHE, mild inattention and deficits of executive function) to overt HE (disorientation to coma). Over 40% of patients with cirrhosis develop HE, which increases mortality, falls, motor-vehicle accidents, and has significant psychosocial impact.[1] Early recognition is crucial. Patients with cirrhosis are recommended to receive an assessment for MHE.[2]

To diagnose MHE, one must consult a neuropsychologist for tests that are administered and scored against local reference data.[2] Point-of-care tests (e.g. EncephalApp) are available but also derive diagnostic cutoffs from the same data.[3] MHE is thus diagnosed by performance relative to age, sex, and (frequently) education-matched controls.[2–4] Data are limited whether cutoffs derived from one population's controls generalize to another. Control performance has been characterized in Mexico and Europe,[4, 5] but representative US data are lacking. Herein, we characterize factors that may confound psychometric tests interpretation in a nationally representative cohort.

Methods

NHANES-III is a nationally representative cross-sectional survey conducted 1988–1994, in which a randomly selected subjects aged 20–59 years (n=4,924) underwent neuropsychometric testing using the Neurobehavioral Evaluation System 2 (NES2).[6] The NES2, a computerized cognitive function battery, consists of three components: simple

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reaction time test (SRTT; measures visuomotor speed), symbol digit substitution test (SDST; measures symbol coding speed), and serial digit learning test (SDLT; measure of working memory and learning). The NES2 is not used for the diagnosis of MHE, however it is very similar to standard psychometric tests.[3] We identified 675 persons with definitive chronic liver disease (CLD), including chronic viral hepatitis (hepatitis C RNA or hepatitis B surface antigen), nonalcoholic steatohepatitis (NASH; hepatosteatosis by ultrasound with abnormal transaminases) and alcoholic liver disease (ALD; >14 drinks weekly and abnormal transaminases). An additional 939 individuals were identified as suspected CLD based on abnormal ALT (male >30 IU/L, female >19 IU/L), AST (>33 IU/L) or ALP (>100 IU/L). We calculated the AST-platelet ratio index (APRI), a sensitive, non-specific fibrosis risk-index. We investigated associations with composite NES2 scores using weight-adjusted univariate and multivariate linear regression.

Results

The cohort represented a national population of 62.1 million adults aged an average 36.9 years, 52% female, and 77% Caucasian. Definitive CLD was present in 11.2% (8.4% NASH, 2.8% viral hepatitis, and 2.6% ALD) and an additional 17.0% had suspected CLD, corresponding to an estimated 14 and 21 million adults aged 20–59, respectively. Definitive and suspected CLD was associated with an increase of 0.26 and 0.24 standard deviation (sd) of the composite NES2 score (worse performance) and 0.14 and 0.14 sd after adjusting for potential confounders.(Table) The magnitude of CLD's association with NES2 score was second to diabetes in multivariate analysis, with the strongest association noted among NASH patients. Other significant associations included age, gender, education, smoking, alcohol, and BMI. Suspected CLD was associated with all NES2 domains (β=0.09, 0.09, and 0.12 sd for SDST, SDLT and SRTT respectively) in multivariate analysis; definitive CLD was significantly associated with the SDST (β=0.12 sd) and SDLT (β=0.12 sd), but not with SRTT components.

Discussion

These data, the first from a nationally representative American cohort, offer three novel findings. First, clinical features of 'healthy controls' such as age, sex, education, BMI, diabetes, smoking, and alcohol influence cognitive test performance. The prevalence of these factors varies substantially between populations but are seldom considered when matching controls to create diagnostic cutoffs for MHE. Second, though few subjects had probable cirrhosis (per APRI), the presence of CLD (ALD, Hepatitis C, or NASH) was associated with worse cognitive performance which suggests that factors beyond cirrhotic physiology may explain the cognitive changes observed in comparison to controls. Third, because comorbidities and specific liver diseases impact cognition independent of cirrhotic physiology, these conditions may affect psychometric test interpretation in afflicted patients with cirrhosis. For example, the vast majority of studies of MHE exclude patients with ALD.[3, 7, 8] Our data suggests that cutoffs derived from non-ALD patients with cirrhosis may not be applicable for those with ALD.

In conclusion, generalizable psychometric testing using reference data requires careful control matching. The impact of CLD itself, alcohol, obesity, diabetes, and smoking on cognitive test performance may deserve future study. The pitfalls of control matching are substantial. To maximize both specificity and generalizability, cutoffs for MHE could be derived not from a proxy – comparing psychometric testing performance to controls - but from clinical outcomes. What matters most about a test is the ability to predict overt HE, not to compare cognitive function with a non-cirrhotic subject. Future studies should determine cognitive test cutoffs using outcome prediction from longitudinal cohorts of patients at-risk for the development of overt HE.

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Table 1

Factors associated with the composite NES Score

	Univariate[1]			Multivariate without CLD			Multivariate with CLD		
	β	SE	P value	β	SE	P value	β	SE	P value
Age 50 year or older (n=776)	0.49	0.04	<0.001	0.41	0.04	<0.001	0.42	0.04	<0.001
Female (n= 2682)	0.09	0.04	0.02	0.03	0.03	0.3	0.08	0.03	0.007
Education									
Less than high school (n=911)	1.06	0.07	<0.001	0.80	0.06	<0.001	0.85	0.06	<0.001
BMI (vs. normal)									
Overweight (25–30) (n= 1544)	0.16	0.04	<0.001	0.06	0.10	0.005	0.09	0.04	0.02
Obese (> 30) (n= 1309)	0.33	0.05	<0.001	0.11	0.15	0.002	0.16	0.05	0.004
Medical history									
Coronary artery disease (n= 67)	0.14	0.07	0.05	0.06	0.06	0.3	0.07	0.05	0.2
Stroke (n= 29)	0.79	0.28	0.007	0.29	0.26	0.3	0.29	0.28	0.3
Diabetes (n= 224)	0.52	0.14	<0.001	0.29	0.11	0.01	0.27	0.12	0.03
Smoking									
Previous smoker (n= 930)	−0.05	0.05	0.3	−0.01	0.04	0.8	−0.07	0.04	0.1
Active smoker (n= 1497)	0.07	0.04	0.06	0.12	0.03	<0.001	0.05	0.03	0.08
Alcohol consumption[2]									
History of alcohol abuse (≥5 drinks daily) (n= 203)	0.42	0.07	<0.001	0.18	0.07	0.02			
Current heavy drinker (≥14 drinks per week) (n= 353)	0.12	0.07	0.08	0.06	0.06	0.3			
Chronic liver disease									
Suspected CLD (n= 939)[3]	0.26	0.05	<0.001				0.14	0.04	0.001
Definitive CLD (n= 675)[4]	0.24	0.07	0.001				0.14	0.06	0.03
Viral hepatitis (n = 152)	0.16	0.10	0.1						
ALD (n = 140)	0.27	0.14	0.06						
NASH (n = 522)	0.22	0.07	0.005						

	Univariate[1]			Multivariate without CLD			Multivariate with CLD		
	β	SE	P value	β	SE	P value	β	SE	P value
Advanced liver fibrosis									
APRI > 1 (n=50)	0.40	0.19	0.04						

ALD = alcoholic liver disease, APRI = ast-platelet ratio index, BMI = body mass index, NASH = nonalcoholic steatohepatitis

A composite NES score is created on the scale of standard deviation in reference to the mean of three NES2 components. Each component of the NES2 was first converted to its Z-score in the unit of standard deviation. For example, the Z-score for the SRTT was derived as follows: ZScore $_{[SRTT]}$ = (SRTT – Mean $_{[SRTT]}$)/Stdev $_{[SRTT]}$. A composite NES score was calculated by the z-score transformation of the sum of three Z-scores of NES2 components: NES Score = (Total ZScore - Mean$_{[Total\ ZScore]}$)/Stdev $_{[Total\ ZScore]}$)

[2]All univariate and multivariate regression analyses were adjusted for sampling weights

[3]Coefficient referenced to mild-to-moderate drinking. Alcohol consumption is excluded in the multivariate analysis with CLD because it was used to define alcoholic CLD

[4]Suspected CLD was defined by abnormal LFT using the following cutoff: ALT (males >30 IU/L, females >19 IU/L), or AST (>33 IU/L) or ALP (>100 IU/L)

[5]Subclasses of CLD were not mutually exclusive.