Original Article

Normalization of the Psychometric Hepatic Encephalopathy score for Diagnosis of Minimal Hepatic Encephalopathy in Turkey

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Abstract

Aim: To construct normal values for the tests of the psychometric hepatic encephalopathy score (PHES) and evaluate the prevalence of minimal hepatic encephalopathy (MHE) among Turkish patients with liver cirrhosis. **Materials and Methods:** One hundred and eighty-five healthy subjects and sixty patients with liver cirrhosis without overt hepatic encephalopathy were included in the study. All subjects underwent psychometric tests, which include number connection test-A and B (NCT-A/B), serial dotting test (DST), line drawing test (LDT), and digit symbol test (DST) in the same day. The variables that affected the results of the test were included in the multiple linear regression models and formulas were constructed to predict the expected results for each tests. **Results:** The results of all PHES tests, except the LDT in the cirrhotic group were significantly different than center of gravity (CG) ($P < 0,001$). The score of PHES in the cirrhotic group was -2,18 ± 3,3 (median -2; range: 11 to +4), significantly lower than CG (-0.31 ± 2.18 [median, 0; range, -8 to +5]) ($P < 0.001$). the cutoff of PHES was set -4 point. Therefore, 19 of the 60 cirrhotic patients were diagnosed with MHE (31.6%). Among the patients with MHE, 11 (11/45, 24,4%) had Child-Pugh classification (CTP) A and 8 (8/15, 53.3%) had CTP B. No differences in age and education years were found between the MHE and non-MHE groups ($P > 0.05$). **Conclusion:** Turkish PHES normograms have been developed for detecting patients with MHE. Future multicenter national studies are needed to validate widely applicable norms.

Keywords: *Cirrhosis, minimal hepatic encephalopathy, psychometric tests*

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Introduction

Minimal hepatic encephalopathy (MHE) is the first phase in the clinical spectrum of HE. It occurs in up to 30-84% of patients with cirrhosis.[1,2] The patients with MHE have deficits in neurocognitive functions such as attention, reaction time, vigilance, coordination, memory, and fine motor abilities. MHE is associated with a reduced quality of life, increased risk of traffic/work accidents and death. MHE also increases the risk of development of overt HE (OHE). Hence, early identification and treatment of MHE are clinically important.[3,4]

MHE is not recognize by routine clinically and laboratory tests. However, it can be only detected by specific psychometric/neurophysiological tests. In 1998, by the working party in World Congress of Gastroenterology recommended that psychometric hepatic encephalopathy score (PHES) was a gold standard test for the diagnosis of MHE.[5] The PHES consists of five pencil and paper tests: The number connection test-A and B (NCT-A/B), the digit symbol test (DST), the serial dotting test (SDT), and the line drawing test (LDT). Each of tests evaluate in different neurocognitive abilities.[6]

The PHES could easily be conducted by clinicians and applied cross-culturally. However, each country should develop normative data from their own cultural background because the results of the PHES tests can be influenced by age, education levels, and gender.[5] Till date, the PHES has been standardized in several countries such as Germany,[5] Italy,[7] Spain,[8] India,[9] Korea,[10] China,[11] and Mexico.[12] Till date, PHES normalization study has never been performed in Turkish population.

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The aims of this study were: (1) To standardize of normal values for the PHES in a healthy Turkish population (2) evaluate the prevalence of MHE among Turkish patients with liver cirrhosis.

Materials and Methods

Control group for normalization of psychometric tests

From June 2014 to October 2015, we recruited 185 healthy volunteers from the general population to establish the distribution of PHES score. The following exclusion criteria were (1) presence of liver diseases; (2) neurological or psychiatric disease, or other diseases that can affect cognitive function; (3) diabetes mellitus; (4) significant comorbid illness such as heart and renal failure consumption of alcohol and psychotropic drugs (5) inability to read and write. Age, sex, and education level were recorded.

The number of volunteers required for reliable distributions of "normal performance" in the PHES across age and education level was assessed by creating three categories for each variable: 30–39, 40-49, 50-59 years, and ≥60 years for age and ≤5, 5-12, and ≥12 years of school attendance for education. In addition, healthy volunteers were selected among individuals in living both in urban and rural areas. Table 1 shows the distribution of healthy subjects (n: 185) in realtion to age groups. Written informed consent was obtained from each subject, and the Local Ethics Committee approved the study protocol.

Psychometric tests

All healthy volunteers underwent a series of psychometric tests, which include NCT-A, NCT-B, DST, SDT, and LDT. There is not difference between the German and the Turkish alphabets. In the NCT-A, patient connect numbers from 1 to 25 printed paper as quickly as possible. Thus, in the NCT-B, the patients connect alternating numbers and letters (1-A, 2-B, 3-C). In the DST, the subjects have to transcribe symbols accurately and quickly corresponding to numbers, looking at a key in a timed manner over 90 s. In SDT, subjects place dots exactly in the center of ten rows a large circles beginning from each row on the left and working to the right. The test score is the time required to complete the test. In LDT, results were calculated as LDT SUM (complete time+errror).[12]

The results (NCT-A, NCT-B, SDT, and LDT) within ±1 standard deviation (SD) from the mean of the control performance were scored as 0 points. Results between ±1 and ±2 SD, between ±2 and ±3 SD, and worse than ±3 SD were scored as -1, -2, and -3 points, respectively. Those better than mean 1 SD were scored as ±1 point.[5,11] The result of DST within ±1 SD from the mean of the control performance was scored as 0 points. Results between -1 and -2 SD, between -2 and -3 SD and worse than -3 SD were scored as -1, -2 and -3, respectively. A result better than mean +1 SD was scored as ±1. The final score of PHES was generated from the sum of the scores of five tests, which ranged between +5 and -15.

Liver cirrhosis group

From June 2014 to October 2015, 85 cirrhotic patients admitted to the Gastroenterology department in Kayseri Training and Research Hospital were screened for MHE. Cirrhosis was diagnosed on histologically or the presence of laboratory tests, endoscopic, and sonographic findings. The staging of cirrhosis was determined by the Child-Pugh classification (CTP) and model of end-stage liver disease (MELD).[8] The exclusion criteria were the presence of OHE, history of taking lactulose or antibiotics, gastrointestinal hemorrhage or spontaneous bacterial peritonitis during the past 30 days, previous transhepatic portosystemic shunt (TIPS) or shunt surgery, hepatocellular carcinoma or other malignancy, alcohol/psychoactive drug intake, poorly controlled diabetes mellitus, significant comorbid illness such as heart and renal failure, neurologic diseases such as Alzheimer's disease or Parkinson's disease, inability to read and write. Patients with visual impairment were not included in the study. Table 2 shows demographic, clinical, and biochemical characteristics of control and cirrhotic patients.

Clinical evaluation of OHE was performed with neurological examination according to West-Haven criteria[7] and the clinical HE staging scale.[13] Totally 15 patients were excluded from the study because OHE (Grade 1 and 2) was diagnosed. In addition, patients who met the inclusion criteria underwent mini-mental state examination and if the score was >25, PHES tests were performed. All psychometric tests were scored by age and education adjusted normograms and the point of each test was collected, and the final score was obtained. The tests were conducted on a one-to-one basis in a quiet room with sufficient light by specially trained medical doctors (BDO and MA).

Laboratory measurements

On the day of neuropsychological testing, venous blood samples for the biochemical measurements were obtained after overnight fasting. Serum was isolated within 2-4 h and transported to the central laboratory for further analysis. Biochemical tests for aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, bilirubin, albumin, total cholesterol, and complete blood count, prothrombin time and

International Normalized Ratio were measured by commercial assays in the clinical laboratory. Venous ammonia concentration was also determined using the Ammonia Checker II (Daiichi Kagaku, Kyoto, Japan).

Statistical Analysis

All statistical analysis were carried out using the SPSS software (version 15, SPSS Inc., Chicago, Illinois, USA). The Shapiro-Wilk normality test was used to assess the normality of the variables' distributions. Continuous variables with a normal distribution were presented as means ± SD. Medians were used when a normal distribution was absent. Parametric variables between two groups were analyzed using Student's *t*-test. The Mann-Whitney U-test was used to compare nonparametric variables between the two groups. Qualitative variables were given as percentages, and the Chi-square test was used to define the differences between the patient groups. Multiple linear regression models were used to predict the value of each test for patients with liver cirrhosis. Correlation analyses were carried out using Pearson's test for parametric variables and Spearman's test was used for nonparametric variables. Multivariate analyses were performed to identify independent variables. A two-sided $P < 0.05$ was considered statistically significant.

Results

Psychometric hepatic encephalopathy score in control group

In total 185 healthy volunteers were involved in this study. The mean age and education of center of gravity (CG) were 46 ± 10.3 and 8,6 ± 3,03 years, respectively and 95 of the subjects were men (51.6%). The distribution of subjects according to age was as follows: 30–39 years, 54 (29.1%), 40–49 years, 63 (34.05%), 50–59 years, 43 (23.2%), and ≥60, 25 (13.5%). Age did not differ between the men and women.

The results of NCT-A, NCT-B, LTT, SDT, and DST were 42.9 ± 19.7, 89.3 ± 37.3, 60.1 ± 16.7, 87.1 ± 11.3, and 33.7 ± 13.4, respectively. The results of NCT-A, NCT-B, and LDT were inversely correlated with education levels, whereas the result of DST and SDT was positively correlated with education levels. The results of NCT-A, NCT-B, and LDT were positive correlated with age, whereas the result of DST and SDT were inversely correlated with age. Gender was not correlated with results of PHES tests. Younger age and better education were associated with better DST and LDT results. The correlations between PHES tests and age and education years are shown in Table 3. Furthermore, in the multivariate analysis, age and education remained significant performance predictors for all five tests in CG. The variables that affected the

Table 1: Distribution of healthy subjects (*n*=185) in relation to age groups

	Gender (male/female) (%)	Educations (years)
30-39 years (*n*=54)	28 K (51.9)/26 E (48.1)	10.7±3.41
40-49 years (*n*=63)	26 K (41.3)/37 E (58.7)	9.7±3.15
50-59 years (*n*=43)	26 K (60.5)/17 E (39.5)	9.2±3.2
≥60 years (*n*=25)	10 K (37.5)/15 E (62.5)	8.7±3.17

Table 2: Demographic, clinical, and biochemical characteristics of control and cirrhotic patients

Baseline parameters	Cirrhosis (*n*=60)
Sex (female/male)	22/38
Age (years)	54.2±8.3
Eğitim (years)	6.2±2.5
Etiology of cirrhosis (%)	
Viral hepatitis	43 (71.7)
Steatohepatitis	5 (8.3)
Alcoholic	3 (5)
Others	9 (15)
WBC (/L)	5.2±2.1
Hb (gr/dL)	12.7±1.9
Platelets (10^9/L)	127.9±70
ALT (U/L)	43.5±36
AST (U/L)	55.5±37.3
Albumin (g/dL)	3.7±0.8
PT (s)	15.4±1.8
Child-Pugh class (%)	
Child A	45 (72.9)
Child B	15 (27.05)
MELD score	9±4.2
Ammonia (μmol/L)	75.6±36.6

WBC=White blood cell; Hb=Hemoglobin; AST=Aspartat aminotransferase; ALT=Alanine aminotransferase; PT=Protrombin time; MELD=Model for end-stage liver disease; s=Seconds

Table 3: Correlations between psychometric tests and age and education years in the control group

	Age		Education	
	R	*P*	*R*	*P*
NCTA	0.530	0.001	-0.342	0.001
NCTB	0.454	0.001	-0.392	0.001
DST	-0.427	0.001	0.604	0.001
LDT	0.076	0.002	-0.295	0.001
SDT	-0.225	0.002	0.229	0.002

The data are presented as Spearman's correlation coefficients. $P<0.05$. NCT-A=Number connection test-A; NCT-B=Number connection test-B; SDT=Serial dotting test; LDT=Line drawing test; DST=Digit symbol test

results of a neuropsychological test were included in the multiple linear regression models and the final formulas are shown in Table 4.

The mean of PHES in the CG was 0.31 ± 2.18 points (median, 0; range, -8 to + 5). The cutoff between the normal and pathological values was calculated at -2 SD of the mean PHES and was set at -4 points. Therefore, MHE was diagnosed when the PHES score was ≤ - 4 points. Two healthy people have pathologic test results. The final PHES score was not correlated with age (P = 0.74) and education years (P = 0.73). In addition, the score of PHES did not differ between men and women (P = 0.589).

Psychometric hepatic encephalopathy score in cirrhotic group

85 cirrhotic patients were screened for MHE. 25 patients were excluded as they fulfilled either one or more of exclusion criteria. Finally, 60 patients with cirrhosis without OHE (age, 54.2 ± 8,3 years, education years, 6,2 ± 2,5 years) were included in this group, 22 of the patients (36.6%) were female. The etiology of cirrhosis was hepatitis B virus in 28 (46,6%) patients, hepatitis C virus in 15 (25%), steatohepatitis in 5 (8.3%), alcoholic in 3 (5%), autoimmune hepatitis in 3 (5%), and cryptogenic cirrhosis in 6 (10%). The CTP score was 5,8 ± 1.4; of the 60 patients, 45 (75%) and 15 (25%) had CTP of A and B, respectively.

The results of NCT-A, NCT-B, LDT, SDT, and DST were 67.3 ± 29.7, 139.4 ± 55,4, 62.6 ± 20.4, 74.6 ± 19 and 20.07 ± 14.9, respectively. In the cirrhotic group, the results of all PHES tests, except the LDT were significantly different than that in the CG (P < 0,001). Table 5 shows the results of psychometric tests in cirrhotic and control group. The mean of PHES in the liver cirrhosis group was -2.18 ± 3.3 points (median -2; range +4 to -11), significantly lower than that in the CG (P < 0.001). Using a cutoff for MHE of ≤-4, 19 of the 60 patients with liver cirrhosis were diagnosed with MHE (31.6%). Among the patients with MHE, 11 (11/45, 24.4%) had CTP A and 8 (8/15, 53.3%) had CTP B. No differences in age and education years were found between the MHE and non-MHE groups (P > 0.05). The PHES was correlated with MELD (r = -0.41, P < 0.001), CTP (r = 0.58, P < 0.001) and PT (r = -0.44, P < 0.01), whereas age, education years and venous ammonia level were not. Education years, Child-Pugh score were independently associated with MHE on multivariate analysis. Table 6 shows the characteristics of patients with or without MHE.

In addition, we calculated PHES using the Spanish reference data (freely available online at www.redeh.org) in all cirrhotic patients and compared the obtained values with Turkish PHES scores. There was a very strong correlation between the two scoring systems (r = 0.543, P < 0.01).

Table 4: Equations for predicting tests results from age and education years in the control group

Tests	Equation	SD
NCT-A	15.956+1.036 × age −2.437 × education	15.399
NCT-B	53.799+1.780 × age −5.449 × education	29.034
DST	37.232−0.585 × age −2.746 × education	9.115
LDT	67.254+0.155 × age+1.662 × education	16.059
SDT	92.202−0.274 × age+0.829 × education	12.125

Age and education are expressed in years. NCT-A=Number connection test-A; NCT-B=Number connection test-B; SDT=Serial dotting test; LDT=Line drawing test; DST=Digit symbol test; SD=Standard deviation

Table 5: The results of psychometric tests in cirrhotic and control group

Testler	Cirrhotic group (n=60)	Control group (n=185)	P
NCT-A	67.3±29.7	42.9±19.7	<0.001
NCT-B	139.4±55.4	89.3±37.4	<0.001
DST	20.07±14.9	33.7±13.4	<0.001
LDT	62.6±20.4	60.1±16.7	0.414
SDT	74.6±19	86.6±12.6	<0.001
PHES	−2.18±3.3 (median−2; range +4 to −11)	0.31±2.18 (median 0; range +5 to −8)	<0.001

NCT-A=Number connection test-A; NCT-B=Number connection test-B; SDT=Serial dotting test; LDT=Line drawing test; DST=Digit symbol test; PHES=Psychometric hepatic encephalopathy score

Table 6: Demographic, clinical, and biochemical characteristics of patients with and without minimal hepatic encephalopathy

Patients	No MHE (n=41)	MHE (n=19)	P
Age (years)	56 ± 8.4	57 ± 7	0.62
Sex (female/male)	32/24	11/18	0.64
Eğitim (year)	6.5 ± 3.3	6.9 ± 3.3	0.03
WBC (/mm3)	4.9 ± 2	5.5 ± 2.2	0.242
Hb (g/dl)	13 ± 2	12.6 ± 1.9	0.41
Plt (10^9/L)	127 ± 80	129 ± 61	0.92
AST (U/L)	55 ± 49	62.6 ± 53	0.08
ALT (U/L)	48 ± 48	49 ± 49	0.25
Albumin (g/dl)	3.7 ± 0.6	3.7 ± 0.9	0.33
PT (s)	16.2 ± 1.7	17.3 ± 2.1	0.45
Ammonia (µmol/L)	65 ± 37	79 ± 33	0.27
Child-Pugh class			
Child A	34	11	
Child B	7	8	

WBC=White blood cell; Hb=Hemoglobin; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; PT=Protrombin time; MELD=Model for end-stage liver disease; MHE=Minimal hepatic encephalopathy; s=seconds

Discussion

Our study was aimed to standardize of normal values for the PHES in a healthy Turkish population and to assess the utility of PHES as a diagnostic tool for the diagnosis of MHE in patients with liver cirrhosis. This study was the first investigation normal values of PHES tests in Turkish population.

In this study, we found that (i) age and education levels were predictors of all PHES tests, therefore, age and education-adjusted normograms were developed, (ii) the mean of PHES was found 0.31 ± 2.18 points (median, 0; range, -8 to +5) and the cutoff for the diagnosis of MHE was set on -4 point, (iii) MHE was diagnosed in 31.6% of patients with liver cirrhosis, (iv) MHE was associated with the severity of liver function and presence of esophageal varices.

PHES was an sensitive, reliable and inexpensive tool for screening patients with cirrhosis for MHE. It can distinguish patients with MHE from those with OHE as well as from healthy subjects.[14] By Schomerus and Hamster PHES had been specifically developed for the diagnosis of MHE.[15] However, since the PHES can be influenced by age and educational status, normative data is needed before applying it to the diagnosis of MHE in populations with different cultural background.[7,8] Weissenborn *et al*. collected the first age-adjusted normative data for the German population.[5] Currently, the PHES has also been widely validated in Spanish,[8] Italian,[7] Mexico,[12] India,[9] China[11] and Korean[10] populations. In this study, PHES score was adjusted using a cohort 185 people drawn from general populations that had been stratified by age, gender, and education level.

A PHES validation studies in Germany[5] and India[9] showed that the age of the patient affects PHES, and subsequent validation studies in Spain, Italy, Mexico, Korea, and China revealed that level of education also influences PHES.[7,8,10-12] In our study, we also observed that the results of all psychometric tests were influenced by age and education years.

Until date, all validation studies, except the Korea and Mexico studies showed that gender did not have any role on the tests performance.[5,7,8,10,11] Gender was only affected the SDT in Korea study while gender was affected the DST and the SDT in Mexico study.[10,12] In our study, gender was also not affected results of all tests. Thus, age and education level were included in the multiple linear regression model and final formulas was occurred.

In accordance with Germany, Spain, Italy, Mexico and China validation studies, we found that the cut off of PHES for diagnosis MHE was ≤-4 point.[5,7,8,11,12] However, validation studies in Poland, India, and Korea were found that the cutoff of PHES for diagnosis MHE was ≤-5 point.[9,10,16] This can be due to (i) use of different score systems for the LDT (LDT_{sum} [complete time + error], two separate results [LDT_{error} and LDT_{time}] or weighted time), (ii) normative data are calculated with different ways (age and education adjusted values in Italy and Spanish[7,8] vs age-adjusted values in Germany and India[5,9] (iii) in the Indian study, NCT-B is replaced with figure connection test, which assesses different cognitive abilities than NCT-B.[9] In the Korean study, $PHES_{Korea}$ was compared with $PHES_{Italian}$ and $PHES_{Spain}$. However, because of the differences in the methods used to interpreted the LDT, its were remeasured using LDT_t and LDT_e: (i) The error-weight time (w-LDT; $LDT_t \times [1 + LDT_e/100]$), and (ii) the sum of LDT_t and LDT_e (LDT_{sum}). The cutoff of $PHES_{Italian}$ and $PHES_{Spain}$ for MHE diagnosis was found >-5 point and the prevalence of MHE was not changed.[10] In the original studies, the cutoff of $PHES_{Italian}$ and $PHES_{Spanish}$ was - 4 point and - 5 point, respectively.[7,10] In our study, the LDT_{sum} scoring system was used, such as Spain and Mexico.[8,12]

Accordingly, patients with liver cirrhosis were diagnosed with MHE on the basis of PHES scores lower than -4. Thus, MHE was diagnosed in 31.6% of patients with liver cirrhosis. Sharma *et al*. reported that the prevalence of MHE in the 110 cirrhotic patients (Child A/B/C: 39/42/29) by PHES was detected 68%, respectively. Of cirrhotic patients with MHE, 44% were in CTP A class, 50% in CTP B class and 76% in CTP C class in this study.[17] Romero-Gómez *et al*. were also reported that the prevalence of MHE in 114 cirrhotic patients (CTP A/B/C: 57/36/21) by PHES tests was detected 30.7%.[18] In this study, we found that the prevalence of MHE by PHES test was lower when compared these studies. This is related to the most of our studied patients were in Child A and no patients in Child C.

In previous studies, the risk factors of MHE was determined as follows; (i) age, (ii) presence of esophageal varices. (iii) TIPS or surgical portosystemic shunts (iv) prior episodes of OHE.[19,20] None of our patients had experienced a previous episode of OHE or had undergone TIPS or surgery portosystemic shunts. However, various results have been obtained in studies on the association between severity of liver disease and MHE. While, Romero-Gómez *et al*.[18] and Kircheis *et al*.[21] showed that the neurologic abnormalities in cirrhotic patients exert little or no relationship with the degree of hepatic disease. Dhiman *et al*.[9] and Taneja *et al*.[22] demonstrated a higher prevalence of MHE in cirrhotics with CTP class C than in cirrhotics with CTP class A and B. We also observed that MHE was moderately correlated with CTP class (r = -0,30, P < 0,05). The prevalence of MHE in cirrhotics

with CTP class B (47%) was higher than in cirrhotics with CTP class A (29%) ($P = 0.03$).

Ammonia has been shown to be an important etiological parameter in the pathogenesis of MHE.[23] Although, the relationship between blood ammonia concentration and HE is still controversial, treatment modalities that decrease ammonia level (for example, lactulose, L-ornithine-L-aspartate, branched-chain amino acids, and probiotics) receive to treat this condition.[24,25] While Sharma *et al*.[24,26] and Kircheis *et al*.[21] demonstrated a significant correlation of venous ammonia level with MHE. In this study, we found that venous ammonia was no significantly differences between MHE patients and non-MHE patients (65 ± 37 vs. 79 ± 33 µmol/l, $P = 0.27$). This is related to the most of our studied patients were in Child A and no patients in Child C.

Conclusion

MHE is the first phase in the clinical spectrum of HE. It is associated with an impaired quality of life, increased risk of traffic/work accidents and death. Therefore, it should be early diagnosed and treated. We found that MHE prevalence in cirrhotic patients was increased and correlated with severity of liver disease. Even cirrhotic patients are in Child A, they should be screened for the diagnosis of MHE and be treated.

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Conflicts of interest

There are no conflicts of interest.

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