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Determination of Normative value of Psychometric Hepatic Encephalopathy Score in Bangladeshi Volunteers

MK PODDER[a], H AFTAB[b], MM KHALIL[c], MI HOSSAIN[d], MI HOSSAIN[e], P ULLAH[f], M FAKRUZZAMAN[g]

Abstract:

Background and Objectives: *The psychometric hepatic encephalopathy score (PHES) is a composite score of five different neuropsychological tests. It is considered as gold standard test to diagnose Minimal Hepatic Encephalopathy(MHE). But one problem with PHES is that it needs normative value of its five components as they vary from population to population. So population based normative value should be derived before it is applied to that population. MHE is diagnosed when variation from this normal value occur, provided other criteria are fulfilled. The aim of this study is to find out the normative value of PHES test batteries.*

Methods: *This cross sectional observational study among healthy volunteers took place in department of Gastroenterology, Dhaka medical college from May 2019 to April 2020. All participants in this study took part in the test according to international norm.*

Results: *Among the 300 study population,age and years of education had significant impact on all tests score. Hence, multivariate equation adjusting age and years of education were derived. A scoring method was applied depending on deviation from predicted score for all tests. Finally, -5 PHES was determined as cut off value for normal and pathological.*

Conclusion: *Age and education adjusted normative value of five components of PHES were constructed in Bangladeshi population. PHES cut off value was also determined. Now it is possible to calculate PHES among liver cirrhosis patients of Bangladesh.*

Key words: *PHES, MHE, Normative value*

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Introduction:

Hepatic encephalopathy occurs both in acute and chronic liver dysfunction due to impaired brain function manifests as neurocognitive disorder[1].It is a major complication that develops in a majority of patients with liver cirrhosis. The prevalence of MHE varies worldwide which ranging from 30 to 84%. Different studies in India reveal prevalence of MHE varies between 48% and 67.7%[1-3]. A study which used 3 out of 5 components of PHES without age and education adjustment revealed prevalence of MHE is 66% in our country[4].This variation may be due to difference in criteria used to diagnose MHE and due to population selected.

Diagnosis of overt hepatic encephalopathy is relatively easy from clinical spectrum and patients are occasionally brought to the clinical facility. Whereas, MHE is subtle neurocognitive deficit which requires special test to diagnose it and often remain unrecognized. In MHE, neurocognitive abnormalities affect attention, speed of information processing, executive control, motor ability and coordination.

Tests which are used to diagnose MHE, can be divided into two major types: psychometric and neurophysiological which includes portosystemic encephalopathy syndrome test, Critical Flicker Frequency test, Stroop test, EEG etc[5]. International Society of Hepatic Encephalopathy and Nitrogen metabolism (ISHEN) group recommends the use of Psychometric Hepatic Encephalopathy Score (PHES) or Repeatable Battery for the Assessment of

a. Dr. Mrinmay Kumar Podder, Junior consultant(Medicine), UHC, Kotalipara,Gopalganj , Bangladesh.
b. Prof. Dr. Hafeza Aftab, Head, Dept. of Gastroenterology, Dhaka Medical College , Dhaka, Bangladesh.
c. Dr. Md Musab Khalil, Assistant Registrar, Sheikh Russel National Gastroliver Institute and Hospital, Dhaka, Bangladesh.
d. Dr. Mohammad Iqbal Hossain, Junior Consultant (Medicine), Sheikh Russel National Gastroliver Institute and Hospital, Dhaka, Bangladesh.
e. Dr. Md. Imran Hossain, MO, Department of Gastroenterology, Sir Salimullah Medical College Hospital, Dhaka, Bangladesh.
f. Dr. Parash Ullah, MO,Department of Gastroenterology, Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh.
g. Dr. Md. Fakruzzaman, Junior Consultant (Medicine), Department of Hepatology, Mymensingh Medical College Hospital, Dhaka, Bangladesh.

Address of Correspondence: Dr Mrinmay Kumar Podder, Junior consultant(Medicine), UHC, Kotalipara, Gopalganj, 49/4, R.K. Mission road, Flat-A4, Dhaka-1203, Mobile: 01741240874, E-mail: mrinmaypodder@yahoo.com

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Neuropsychological Status (RBANS) test to diagnose MHE[6].Between this two, PHES is mostly used.

PHES consists of five tests which are Digit symbol test (DST), Number connection test A(NCT A) or Trail Making Test A(TMTA),Number connection test B(NCTB),Serial dotting test (SDT), Line tracing test (LTT) for time and error. Figure connection test A may replace NCTB if it is to be used in illiterate persons[7].They evaluate cognition, psychomotor processing speed and visuomotor coordination. MHE is clinically significant as it impairs daily activities, work performance, driving ability and health-related quality of life, as well as increase the risk of falls.MHE may turn into overt hepatic encephalopathy[8].So, it's diagnosis is important. But it's diagnosis is underestimated most of the time. PHES test is simple, takes only 15 to 20 minutes, can be done at bedside, cost effective, highly sensitive and specific. One of the main limitations of the PHES is that it has inter-population variations being influenced by factors such as age, education. It is therefore necessary to determine the PHES in a specific population before using it to diagnose MHE. Multivariate equation adjusted with predictors from healthy volunteers for each test is necessary for PHES determination and 2 SD along pathological direction from healthy volunteer mean is the cut off value for determining PHES. So normative value of PHES should be determined first. Normative database for PHES is available in many countries like India[2], China[9], Mexico[10], Italy[11], UK[12], Spain[13], Korea[14], Germany[15] etc. To far known, normative value of PHES to diagnose MHE in our country is yet to be determined. Therefore, this study was done to detect normative value of PHES among Bangladeshi population.

Methods:

This hospital based cross sectional, observational study was carried out in the department of Dhaka medical college hospital, Dhaka, Bangladesh from May 2019 to April 2020.Variables of the study were five components of PHES namely Digit Symbol Test (DST), Trail Making Test A (TMTA), Figure Connection Test A (FCTA), Serial Dotting Test (SDT), Line Tracing Test for time (LTTt), Line Tracing Test for errors (LTTe), age and education. During this period data were collected from the healthy volunteers who accompanied patients and used to work in the department through a questionnaire. Healthy adults more than 18 years were included initially and excluded if found having any evidence of liver or renal diseases, neurological or psychiatric diseases, Use of psychotropic drugs, alcohol consumption, autoimmune diseases or chronic inflammatory diseases, drug abuses, uncontrolled diabetes, family history of liver diseases, inability to read and write, who can not mention exact birthday, visual disturbances not corrected by glass.

Written consent was taken from all participants after informing the scope, limitation and confidentiality issue of the study. They had the right to withdraw them from the study at any time, for any reason. The study did not cause any physical, mental or social harm to healthy volunteers. Ethical committee of Dhaka Medical College and Hospital approved the protocol.

General objective of the study was to find out the normative value of psychometric hepatic encephalopathy score in Bangladeshi population. The Specific objectives were to determine normative values of Digit symbol test, Trial making test A, Figure connection test A. Serial dotting test. Line tracing test.

Total 300 healthy volunteers were included in study completed five components of PHES in sequential manner after appropriate explanation, demonstration and training. DST,TMTA, SDT, LTT and FCTA collected from previous study[7,16]. International recommendation was followed during the performance of tests.

- DST procedure: In DST, different symbols were given under different number. At first subjects were instructed to put symbol as soon as possible in blank space accordingly in practice space. Then subjects were given 90 seconds to fill the blank in real test. Correctly filled spaces were the score.
- TMT A procedure: In this test, subjects drew line from 1 to 25 sequentially as early as possible, any error were corrected by investigator during procedure. Score was completion time including error time.
- FCT A procedure: This test resembles TMT A but sequence varies among five sets of symbol. Score was completion time including error time.
- LDT procedure: Subjects were instructed to draw line in between two parallel lines as soon as possible without touching. Time required is LTTt. LTTe was determined putting transparent sheet for error on LDT sheet. LDT is summation of LTTt and LTTe.
- Data were entered by investigator and accuracy was cross-checked randomly. Statistical analysis was done by SPSS (Statistical Program for Social Science) version-23. Data were expressed as mean±SD. Normality distribution for DST, TMTA, FCTA, SDT, LDT were checked. Log transformation was done for those who were not normally distributed. Bivariate

analysis was done to detect significant predictors. Final multivariate equation was made with age and education years as predictors. Then predicted score for each component of PHES for every healthy volunteer determined. Thereafter, following equation was applied to find out deviation from predicted value for each subsets of PHES among every individual: (predicted value-observed value)/SD. For each test highest score +1 and a result e" 1SD was scored as +1. For each test lowest score -3 and a result d"-3 SD were scored as -3.Results in between +1 and -1 were scored as 0,results -1SD and -2SD above were scored as -1, results -2SDs and -3SDs above were scored as -2.So, PHES scale ranges from +5 to -15. PHES calculated for every volunteers and their mean and SD were calculated. < -2 SD from mean PHES, considered cut off for normal and abnormal.

Results:

A total of 300 healthy volunteers were included in this study.

Table-I

Distribution of the study subject by demographic characteristics (n=300)

Characteristics	n (%)
Age in years	
Mean ± SD (33±9.7)	
Range(18-74)	300(100)
18-30	136(45.3)
31-40	119(39.7)
≥41	45(15)
Sex	
Male	189(63)
Female	111(37)
Education in years	
Range 1-5	36(12)
6-12	103(34.3)
>12	161(53.7)
Mean±SD	12.7±5.07
Occupation	
*White collar	135(45)
**Blue collar	142(47)
Unemployed	23 (7)

*White collar: clerks, students, teaching assistant, office based job,

**Blue collar: farmers, labours, nurses, hospital technical staff

LDT was derived from summation of LTTt and LTTe. Normality distribution of DST, TMTA, FCTA, SDT, LDT were checked. As TMTA, FCTA and SDT not normally distributed, log transformation was done.

Table-II

Correlation of different component of PHES with age and education among study population

Predictors	DST	TMTA	FCTA	SDT	LDT
Age	-0.357*	0.301*	0.355*	0.220*	0.305*
Education	0.625*	-0.625*	-0.566*	-0.526*	-0.451*

Here, * means significant, p<.05. Presented as Pearson's correlation coefficient

Table II shows the results of bivariate analysis to determine the variables affect different neuropsychological test. Results for all tests are significantly correlated with age and education, although in opposing directions.

For above reasons, subsequent multiple linear regression models are constructed to determine beta coefficients included only age and years of education.

Table-III

Multivariate equation of five components of PHES(n=300)

Test	R	R square	SD	Equation
DST	0.799	0.638	6.4436	26.416-.332xage+1.510x education
TMTA	0.675	0.455	0.13079	1.876+.005xage-.021xeducation
FCTA	0.647	0.419	0.15963	1.921+.007xage-.022xeducation
SDT	0.556	0.310	0.09357	1.785+.002xage-.011xeducation
LDT	0.527	0.278	20.29674	124.229+.668xage-2.025xeducation

Table III shows age and education adjusted multivariate equation of each component of PHES.

Table-IV

PHES characteristics among study population(n=300)

PHES	Value
Mean	-0.0367
SD	2.00217
2SD from mean	-4.03 to +3.96
Range	-8 to +5
Cut off value	-5

Table IV shows 2 SD from mean, -4.03 to +3.96. Here, -4.03 is along the pathological direction. As there is no fraction in PHES, next value which is -5 was considered as cut off for healthy and abnormal.

Discussion:

This cross sectional observational study was done to determine PHES in healthy volunteers attending in department of Gastroenterology during the study period. MHE is cognitive impairment in patients with cirrhosis where overt hepatic encephalopathy and other causes of cognitive impairment are excluded[17]. Cognition depends on socio-cultural environment, daily living activities, language etc. It has many domains like psychomotor function, attention, visuospatial ability etc. Interpreting different domains based on the aforementioned factor is necessary for categorising it. Hence, routine clinical tests rarely diagnose cognition. Neuropsychological tests or batteries are used to assess cognition.

ISHEN recommends two batteries for MHE detection, PHES and RBANS. Between this two, PHES is commonly used. As normal values of PHES component vary according to culture, custom, language etc they should be standardized for the population in which they are intended to be used. Among the different predictors, age and education mostly vary PHES. Others, less influencing predictors may be sex, occupation. Hence it needs age and education adjusted normative value according to population. Normative database for PHES is available in many countries like India[2], China[9], Mexico[10], Italy[11], UK[12], Spain[13], Korea[14], Germany[15], Poland[18] etc. PHES 2 SD along pathological direction from healthy volunteers mean is considered as cut off value between normal and pathological. MHE is diagnosed among cirrhotic patients using this cut off value whenever other criteria are fulfilled.

Among the five tests of PHES, raw data of DST and LDT are normally distributed, others are not. A finding mentioned in previous studies[10,11,18]. Log transformation was done for TMTA, FCTA and SDT in accordance with the study of Italy, Germany and Poland.

LTT time and errors are related to one another so that LDT is determined by summarizing time and errors as per Mexican and Spanish studies.

At bivariate analysis age, education level was significant predictors of all test for psychometric performance. This finding is consistent with most of the previous studies from India[2], China[9], Mexico[10], Germany, Italy[11], UK[12], Spain[13], Korea[14], Poland[18]. Age, education adjusted multi-variate equation of five components of PHES are derived. DST is inversely related to age and proportional to education. Score for TMTA, FCTA, SDT, LDT are proportional to age and inversely proportional to education. These findings mirror similar studies. A scoring system was applied based on the deviation from expected value as per previous studies. Age and education does not show correlation with final PHES which found in previous studies and proves its standardization[9,10,18].

Finally, cut off for PHES was determined d" -5. PHES cut off value for diagnosing MHE is -5 in India, China, Korea, Germany, Poland, Spain etc. As this is most commonly found PHES score, Mexican study considered PHES d" -5 for diagnosis of MHE rather than calculating it. This is another evidence of standardizing PHES. Among healthy volunteers 2% have PHES d" -5. This findings are consistent with all other studies. This outlier mostly from rural area and with low educational qualification. Few might have some unrecognised pathological condition.

Conclusion:

This study constructed age and education adjusted normative value of all components of PHES namely DST,TMTA,FCTA,SDT,LDT among Bangladeshi volunteers. Now it is possible to calculate individual component of PHES and from them final PHES among liver cirrhosis patients. PHES cut off value was also determined and was found d" -5. With this value and score it would be possible to diagnose minimal hepatic encephalopathy provided other criteria are fulfilled. This study is a single centre study and sample size is small. Hence, few intra-population variation may exist.

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