

PHES: RELIABLE, BED SIDE DIAGNOSTIC TOOL IN IDENTIFICATION OF MINIMAL HEPATIC ENCEPHALOPATHY

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ABSTRACT

BACKGROUND

Hepatic Encephalopathy (HE), is a neuropsychiatric, progressive and reversible disorder and spectrum ranges from presymptomatic Minimal Hepatic Encephalopathy (MHE) to symptomatic Overt Hepatic Encephalopathy (OHE). The aim of the study is to report the usefulness of Psychometric Hepatic Encephalopathy Score (PHES) in the identification of the MHE patients.

MATERIALS AND METHODS

In this prospective observational randomized case-controlled analysis of data from June 2017 to December 2017, 196 patients met the inclusion criteria of the study. Out of 196 patients, 103 patients were in the control arm and 93 patients were in the study arm. We report the sensitivity, specificity, positive predictive value, negative predictive value of the PHES profile in comparison with EEG.

RESULTS

In our study, the demographic profile in cirrhotics and normal population showed significant difference in the mean age 57.45 ± 6.45 vs 48.10 ± 10.86 ($p < 0.01$), education years 9.68 ± 2.22 vs 11.33 ± 2.64 ($p < 0.01$), and blood ammonia levels 64.84 ± 52.94 vs 30 ± 12.30 ($p < 0.001$). In the PHES variable, there is significant difference ($p < 0.01$) in the study and control group, in PHES: Digital Symbol Test (DST), Number Connection Test-A (NCT-A), Number Connection Test-B (NCT-B), Serial Dotting Test (SDT), Line Tracing Test (LTT) and Total PHES score. The PHES profile of cirrhotic patients in the study group with and without minimal hepatic encephalopathy were respectively, PHES: DST 18.88 ± 7.08 vs. 19 ± 7.6 ($p < 0.01$), PHES: NCT-A 67.13 ± 28.52 vs. 53.88 ± 28.52 ($p < 0.01$), PHES: NCT-B 245.44 ± 43.78 vs. 190.63 ± 88.25 ($p < 0.01$), PHES: SDT 92.43 ± 30.08 vs 78.6 ± 30.31 ($p < 0.01$), PHES: LTT 161.6 ± 51.14 vs 130.01 ± 51.41 ($p < 0.01$), and total PHES score -6.42 ± 5.7 vs. -2.35 ± 5.76 ($p < 0.01$). The serum ammonia level was significantly increased in MHE group as compared to control, and non-MHE group and there is positive correlation between blood ammonia level and Total PHES Score.

CONCLUSION

Bed side PHES score can be used as a diagnostic tool to identify minimal hepatic encephalopathy patients and it shows positive correlation with blood ammonia level and EEG changes.

KEYWORDS

Minimal Hepatic Encephalopathy, Overt Hepatic Encephalopathy (OHE). Psychometric Hepatic Encephalopathy Score, Cirrhosis, Electroencephalograph (EEG).

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BACKGROUND

Hepatic encephalopathy (HE), a complex neuro-psychiatric, disorder is a complication of advanced liver disease. This

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complication can develop in about 30-45% of the cirrhotics at any point of time.¹ Two major determinants for this syndrome are liver parenchymal dysfunction and portosystemic shunt. Spontaneous portosystemic shunts are more prevalent in patients with hepatic encephalopathy as compared to patients with other forms of decompensation like ascites.² Similarly, cognitive impairment is more common in advanced liver disease (Child's C) than in Child's A cirrhotics.³

Spectrum of HE ranges from presymptomatic minimal hepatic encephalopathy (MHE) to symptomatic overt hepatic encephalopathy (OHE). Minimal hepatic encephalopathy is a constellation of cognitive and neuro-physiological

abnormalities presented in patients with liver diseases with a normal clinical and neurological examination and clear mental function.⁴ Decompensation of chronic liver disease in the form of hepatic encephalopathy confers a worse prognosis.

One of the retrospective studies showed survival probability of 42% at 1 year and 23% at 3 years after presenting with an encephalopathy episode.⁵ Hepatic encephalopathy even in its clinically inapparent form i.e., MHE, hampers skilful activities and reduces quality of life. Working Party on hepatic encephalopathy described three different patterns. Most common form is type C; HE associated with chronic liver disease. Type A is described in patients with acute liver failure and type B in patients with portosystemic shunts in absence of liver disease.⁶ 'Ammonia toxicity' as the central mechanism for hepatic encephalopathy stood test of time.

People are now becoming interested to detect the HE at an early stage so that its management can improve the quality of life and delay the development of further complications.⁷ Evidences are coming up in favour of managing minimal hepatic encephalopathy aggressively.^{8,9} Since the liver disease status is the major determinant of appearance and progression of hepatic encephalopathy, improvement in liver function either with antiviral therapy or any other mean is essential component of management of hepatic encephalopathy.

Aim of the study is to show usefulness of bedside PHES scoring system in the identification of patients with minimal hepatic encephalopathy in resource poor country like India and the results were compared with gold standard investigation EEG.

MATERIALS AND METHODS

This prospective observational randomized case-control study was conducted, in the department of Internal Medicine, Civil Hospital Ahmedabad, Gujarat, India over a period of 3 months between June 2017 to December 2017. The patient included in this study were those admitted in the medical wards of Civil Hospital, Ahmedabad as well as those on outpatient treatment.

In this prospective observational randomized controlled study, we included 196 patients with 93 patients in cirrhotic (study) group, taken from both indoor and outdoor department of internal medicine and 103 patients in the control arm (normal population). Out of 93 patients 70 patients were found to have minimal hepatic encephalopathy and rest 23 patients did not have minimal hepatic encephalopathy by PHES. Relatives of the cirrhotic patients were included in the control arm. Written informed consent was obtained from all the participants.

Control Group

People without any abnormal liver or renal function, absence of any chronic liver,¹⁰⁻¹⁴ renal, neurological or psychiatric disorder, and other diseases that can affect cognitive function were included in the study. Those formed standardized PHES sample.

Study Patient Sample

Patients with liver cirrhosis without OHE were included in the study population. Patients were considered as having liver parenchymal disease if ultrasonography abdomen finding was suggestive of coarse or altered echotexture of the liver, splenomegaly, endoscopy showing oesophageal varices.¹⁵

Inclusion Criteria

1. Patients with liver parenchymal diseases.
2. Patients with age >13 years.

Exclusion Criteria

1. Patients with MMSE score <24
2. West haven grading 1-4
3. Patients not willing to participate in the study.

Relevant history, physical examination and systemic examination findings pertaining to liver disease were documented from both study and control arm. All patients were subjected to investigations like ultrasonography Abdomen, psychometric hepatic encephalopathy scoring test (PHES), Electro Encephalography (EEG), Mini Mental Status Examination (MMSE), complete hemogram, Random blood sugar, Renal function test, Liver function test and viral markers (anti HCV antibody, HbsAg), lipid profile. Sample were preserved for autoimmune liver profile, Wilson disease in case of diagnosis not confirmed by aforementioned tests.

Patient with West Haven grade 1 to 4 were excluded from the study population as they are considered to have overt hepatic encephalopathy.

Neuropsychology Testing

Psychometric Hepatic Encephalopathy Scoring Test (PHES)

PHES is composed of 6 subtests; DST (Digital symbol test), NCT-A (Number connection test-A), NCT-B (Number connection test-B), SDT (Serial dotting test), LTT (Line tracing test) -LTTt + LTTe).

Among these DST was measured as point, NCT-A, NCT-B and SDT were measured as seconds and LTT was measured as time to complete (LTTt) + error score (LTTe). PHES final score was calculated by using calculator available at <http://www.redeh.org/phesapp/datos.html> which uses above mention 6 subtests, age and education in years. Highest score of each subtest is 1 and lowest score is -3, thus can score between +6 to -18. Patients are considered in minimal hepatic encephalopathy if score is between -6 to -18.

Electro Encephalography (EEG)

EEG was used as gold standard tool to diagnose MHE.¹⁶ In patient with MHE there was decreased wave frequency and increased wave amplitude, appearance of Theta wave with frequencies between 4-7 cps occurs and delta wave with frequency of 1-3 cps.¹⁶ However there is no correlation between grade of hepatic encephalopathy and EEG changes.

Statistical Analysis

Results were expressed as mean ± SD. Analysis were done using chi-square test, ANOVA test and student unpaired t-test as appropriate. PHES score of cirrhotic and healthy as well as among cirrhotics those who were in MHE and Non-MHE were compared. Then we compared sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PHES scoring system with EEG findings. We also compared blood ammonia level between case and control group and in study arm between MHE and non-MHE group. We also found correlation between PHES and ammonia value.

Blood Ammonia Measurement

A free-flowing venous blood sample was collected in to specimen tube with EDTA containing as anticoagulant. The

sample was analysed by enzymatic method with the use of absorbance spectroscopy.

RESULTS

The demographic profile in cirrhotics and normal population showed significant difference in the mean age 57.45 ± 6.45 vs 48.10 ± 10.86 (p<0.01), education years 9.68 ± 2.22 vs 11.33 ± 2.64 (p<0.01), blood ammonia levels 64.84 ± 52.94 vs 30 ± 12.30 (p<0.001), and non-significant difference in gender (male) 89% vs 79% (p=0.06) in cirrhotic patients and normal population, respectively. Among cirrhotic patients, 54.8% were having alcoholic liver disease, 22.5% were having chronic hepatitis B, 10.7% were having chronic hepatitis C, 20.4% were having cryptogenic cirrhosis and 2.1% were having other disease like Non-alcoholic steatohepatitis and autoimmune hepatitis (Table 1).

PHES: Psychometric Hepatic Encephalopathy Scoring Test

	Cirrhotics (n=93)	Controls (n=103)	P
Age	57.45 ± 7.12	48.10 ± 21.72	<0.01
Sex (male)	89%	79%	0.06
Education (years of schooling)	9.688 ± 4.44	11.33 ± 5.3	<0.01
Aetiology of Liver Cirrhosis Alcohol/B/C/Cryptogenic/Others	45/21/10/25/2		
Child Pugh Class A//B/C	65/28/0		
Ammonia Level (mcg/dl)	64.84 ± 52.94	30 ± 12.30	<0.01

Table 1. Distribution of Age, Sex, Education, Aetiology, Child-Pugh Class and Ammonia Level among the Control and Cirrhotics

B: Chronic hepatitis B; C: Chronic hepatitis C; Others includes autoimmune hepatitis, Nonalcoholic Steatohepatitis (NASH), etc.,

In the PHES variable, there is significant difference in the study and control group in PHES: DST 19.24 ± 7.12 vs. 13.03 ± 8.88 (p<0.01), PHES: NCT-A 67.13 ± 28.52 vs. 57.31 ± 5.96 (p<0.01), PHES: NCT-B 245.44 ± 43.78 vs 172.81 ± 87.56 (p<0.01), PHES: SDT 92.43 ± 30.08 vs. 80.92 ± 19.98 (p<0.01), PHES: LTT 161.6 ± 51.14 vs. 104.6 ± 17.96 (p<0.01), Total PHES score -6.42 ± 5.7 vs. -3.33 ± 2.5 (p<0.01) (Table 2).

PHES Tests	Cirrhotics (n=93)	Controls (n=103)	P
PHES: DST	19.24 ± 7.12	13.03 ± 8.88	<0.01
PHES: NCT-A	67.13 ± 28.52	57.31 ± 5.96	<0.01
PHES: NCT-B	245.44 ± 43.78	172.81 ± 87.56	<0.01
PHES: SDT	92.43 ± 30.08	80.92 ± 19.98	<0.01
PHES: LTT	161.6 ± 51.14	104.6 ± 17.96	<0.01
PHES TOTAL SCORE	-6.42 ± 5.7	-3.33 ± 2.5	<0.01

Table 2. Distribution of PHES Variables among the Control and Cirrhotics Patients

DST (Digital Symbol Test), NCT-A (Number Connection Test-A), NCT-B (Number Connection Test-B), SDT (Serial Dotting Test), LTT (Line Tracing test), PHES (Psychometric Hepatic Encephalopathy Scoring Test).

The distribution of age 56.69 ± 12.96 vs. 59.87 ± 12.90 (p<0.05), gender (male) 74.69% vs. 25.3% (p=0.71), education 9.261 ± 4.48 vs. 10.53 ± 4.46 (p<0.05), blood ammonia level 69.12 ± 57.74 vs. 50.18 ± 19.82 and child Pugh A/B/C 45/25/0 vs. 20/3/0 (p<0.05) class among cirrhotic patients with and without minimal hepatic encephalopathy were respectively in the study group (Table 3).

	MHE (n=70)	NON-MHE (n=23)	P
Age	56.69 ± 12.96	59.87 ± 12.9	0.043
Gender (Male)	74.69%	25.3%	0.7
Education (years)	9.261 ± 4.48	10.53 ± 4.46	0.024
Child pugh (A/B/C)	45/25/0	20/3/0	0.0397
Ammonia	69.12 ± 57.74	50.18 ± 19.82	<0.001

Table 3. Age, Gender, Education, Child Pugh Class and Ammonia Levels Among Cirrhotic Patients with and without Minimal

The PHES profile of cirrhotic patients in the study group with and without minimal hepatic encephalopathy were respectively, PHES: DST 18.88 ± 7.08 vs. 19 ± 7.6 (p<0.01), PHES: NCT-A 67.13 ± 28.52 vs. 53.88 ± 28.52 (p<0.01), PHES: NCT-B 245.44 ± 43.78 vs. 190.63 ± 88.25 (p<0.01), PHES: SDT 92.43 ± 30.08 vs. 78.6 ± 30.31 (p<0.01), PHES: LTT 161.6 ± 51.14 vs. 130.01 ± 51.41 (p<0.01), and total PHES score -6.42 ± 5.7 vs. -2.35 ± 5.76 (p<0.01) (Table 4).

Minimal Hepatic Encephalopathy (MHE)

	MHE (n=70)	NON MHE (n=23)	p
PHES: DST	18.88 ± 7.08	19 ± 7.6	<0.01
PHES: NCT-A	71.49 ± 28.68	53.88 ± 28.52	<0.01
PHES: NCT-B	263.45 ± 87.66	190.63 ± 88.25	<0.01
PHES: SDT	96.98 ± 30.26	130.01 ± 51.41	<0.01
PHES: LTT	171.98 ± 51.38	130 ± 51.41	<0.01
PHES TOTAL SCORE	-7.76 ± 5.72	-2.35 ± 5.76	0.01

Table 4. PHES Profile of Cirrhotic Patients with and without Minimal Hepatic Encephalopathy

DST (Digital Symbol Test), NCT-A (Number Connection Test-A), NCT-B (Number Connection Test-B), SDT (Serial Dotting Test), LTT (Line Tracing Test), PHES (Psychometric Hepatic Encephalopathy Scoring Test)

The mean, median, maximum and minimum ammonia levels in child Pugh class A were 53.36 ± 53.74, 54, 116, 40 and in class B were 87.93 ± 55.06, 56.5, 184, 61, respectively (p<0.01) (Table 5).

Child-Pugh Class	Serum Ammonia Levels			
	Mean	Median	Maximum	Minimum
Class -A	53.36 ± 53.74	54	116	40
Class -B	87.93 ± 55.06	56.5	184	61

Table 5. Comparative Observation in Cirrhotic Patients between Child PUGH Class and Blood Ammonia Level

The serum ammonia level was comparable among control, MHE and non-MHE group with F and f critic value were 111.4265 and 3.042717, respectively.

There is a positive correlation between blood ammonia level and PHES Total Score with r value of 0.54.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the PHES scoring system as compared to EEG in our study group were 90%, 69.56% 90% 69.56 respectively.

DISCUSSION

Hepatic encephalopathy (HE) is a neuropsychiatric disorder that is characterized by a wide spectrum of abnormalities affecting cognition, attention, functional ability, personality and intellect.¹⁷ It is a progressive and reversible disorder which can occur in both acute and chronic liver disease diagnosed after exclusion of other known brain disease. Heterogeneity and variability in the neurologic manifestations of this disorder and by the presence of concomitant precipitating factors makes diagnosis and grading of HE difficult. As far as the severity assessment of HE is considered, no single parameter or index has been shown to be infallible till date.¹⁸ The nomenclature broadly categorizes HE by the nature of hepatic abnormality into

three types, type A is associated with acute liver failure, type B is associated with portal-systemic bypass and no intrinsic hepatocellular disease, type C is associated with cirrhosis and portal hypertension and/or portosystemic shunts. The West Haven criteria are widely used for grading of HE. Grading of HE from I to IV is based on level of consciousness, intellectual function and behaviour.¹⁵ In cirrhosis patients, acute encephalopathy ensues that causes change in mental status and is usually associated with a precipitating factor. Recurrent encephalopathy is seen in cirrhosis patients manifesting as recurrent episodes of an altered mental state occurring in the absence of precipitating factors.

Minimum hepatic encephalopathy (MHE) is a constellation of cognitive and neurophysiological abnormalities present in cirrhosis of liver with a normal clinical neurological examination and clear mental function. The closely-related clinically detected syndrome and which is often predated by MHE is overt hepatic encephalopathy (OHE). Stage 1 OHE and MHE often merge in the continuum of HE, are difficult to differentiate reproductively based on standard psychometric test and are often described together by the term low grade hepatic encephalopathy.^{16,19} Predominant functional abnormalities in MHE include reduced attention span and concentration, learning impairment, memory disturbance, executive disability and psychomotor slowing. MHE is present in 50% of cirrhotic patients. It antedates florid hepatic encephalopathy in 50%. Management of MHE retards and slows down the development of OHE and improves the quality of life. The primary modality for diagnosis of MHE is the psychometric tests like number connection test A (NCT-A), number connection test B (NCT-B), digital symbol test (DST), serial dotting test (SDT), line tracing test (LTT) and total Psychometric hepatic encephalopathy score from previously mentioned subtest. Results of these tests are influenced by the age, education. Despite these limitations, psychometric tests still remain the mainstay in recognition of MHE. More objective assessment can be obtained from the spectral analysis of the electroencephalogram (EEG).

MHE can be diagnosed by other objective tests like²⁰ FDG PET scan,¹⁷ N-NH₃ PET scan, and MR spectroscopy. Despite the objectivity and usefulness, the expenses and non-availability of such tests in usual settings limit their clinical usefulness and necessitate the development of easy and bed side tool for detection of MHE.²⁰

The current study results evaluate the pertinence of PHES for the diagnosing of MHE in context of EEG. In the control sample, we found that all 6 subtests of PHES were impacted by age and years of education. Age and literacy measured as years of education have significant association with PHES performance.²¹ However, no such association was found with gender. PHES showed optimal sensitivity and specificity for diagnosing MHE when diagnostic cut off was set at ≤ -6 . In comparison with control arm, cirrhotic patients were older with mean age of 57.47, had lesser education years with mean of 9.68 years. There wasn't any difference identified in the gender. PHES total score and subtests showed statistically significant difference among cirrhotic population with mean score -6.42, in comparison to control arm. In study population, in comparison to non MHE group, MHE group showed statistically significant difference in age and education years with mean age 56.69 years vs. 59.87 years and mean education years were 9.261 years vs 10.53 years, respectively. No similar difference was noticed in gender. In MHE group, 35.71% patients were in child Pugh class B and 64.28% patients were in child Pugh class A whereas in non MHE group 13.3% patients were in class Band 86.95% patients were in child Pugh class A which was statistically significant. MHE prevalence has a direct correlation with Child-Pugh grade which is evident from

previous studies.^{22,23} We also showcased that MHE patients have a higher trend for Child-Pugh score. We should take care of cirrhotic patients without MHE since the severity of chronic liver disease is likely to be progressed. Among them some patients may eventually develop MHE. We found that PHES is a worthy tool to detect neuropsychiatric dysfunction in cirrhotic patients. PHES profile showed statistically significant difference in MHE group in comparison to non-MHE group. Considering EEG as gold standard,¹⁶ we found sensitivity and specificity of PHES, 90%, 69.56%, respectively.

The pathogenesis of HE is heterogeneous and cannot be accounted to a single factor. Hyperammonaemia, glutamine, nitrous oxide, cGMP, and interleukin-6 are considered to play synergistic roles in HE in inducing its neurological manifestations.²⁴ Serum ammonia levels are reported to be correlated with the degree of encephalopathy.^{25,26} We also identified that ammonia levels were higher in MHE group than non MHE group than control group, which may support that ammonia had association with cognitive impairment in liver cirrhosis.²⁷ Although ammonia play a significant role in the pathogenesis of HE/MHE,²⁸ no any direct consistent correlation is observed between the blood ammonia level and the severity of HE.²⁹ In the current study cohort, patients had been diagnosed as cirrhosis by endoscopy showing oesophageal varices, and abdominal imaging study (splenomegaly with signs of liver cirrhosis like altered liver surface echotexture in ultrasonography). To diagnose chronic liver disease including cirrhosis, pathologic examination of percutaneous biopsy specimens is considered to be the golden standard. However, as this procedure is invasive so is not indicated for patients having bleeding diathesis, ascites and patients with unstable vitals and hence the abdominal imaging studies remain the primary investigation of choice. Furthermore, non-invasive methods to diagnose hepatic fibrosis in the patients of chronic liver disease are highly accurate.³⁰ When there is sufficient uncertainty about diagnosis, severity of disease, prognosis, and treatment decisions or imaging studies and blood investigations do not corroborate then only liver biopsy is advised.³¹ Therefore, clinical diagnosis instead of liver biopsy was mainly used for cirrhosis in our study and all recent studies in the PHES validation for MHE. However, we agreed that this approach may underestimate the diagnosis of liver cirrhosis resulting in overestimation of MHE prevalence.

The PHES has been proven to be of diagnostic as well as prognostic use. A pathological PHES was shown to be predictive for both, the occurrence of an episode of overt HE and survival and to be able to identify cirrhotic patients who are at risk of falls within 1 year after the testing. The PHES as well as the results of the sub-tests show a significant correlation to the cerebral glucose utilization in patients with liver cirrhosis and grades 0–II HE, indicating the ability of the PHES to represent cerebral dysfunction in these patients.

To summarize, the PHES could be a simple and useful bedside diagnostic as well as prognostic tool to detect MHE and monitor its prognosis among cirrhotic patients. Around

two third of cirrhotic patients were identified to have MHE based on a PHES score < -5.

Chronic liver disease is one of the most prevalent condition with variable manifestations and complications with high morbidity and mortality. The major causes of the mortality in chronic liver disease are mainly hepatic encephalopathy and bleeding manifestations.

CONCLUSION

In resource poor regions like South East Asia, bed side PHES with high sensitivity, specificity, PPV and NPV as compared to EEG, with higher cost effectiveness, can be utilized as a reliable diagnostic tool to identify minimal hepatic encephalopathy patients and it shows positive correlations with blood ammonia and EEG changes.

Abbreviation

HE - Hepatic Encephalopathy, OHE - Overt Hepatic Encephalopathy, MHE - Minimal Hepatic Encephalopathy, PHES - Psychometric Hepatic Encephalopathy Score, DST-Digital Symbol Test, NCT-A – Number Connection Test-A, NCT-B- Number Connection Test-B, SDT- Serial Dotting Test SDT, LTT- Line Tracing Test.

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