BMC Neurology

RESEARCH

Open Access

The role of multifocal visual evoked potential in detection of minimal hepatic encephalopathy in patients with compensated liver cirrhosis

Reem M. Sabry[1*], Osama Hamad[2], Hossam Eldin Mohamed Khalil[3], Sahar Ibrahim Mohammed[3], Ragaey Ahmad Eid[2] and Hanan Hosny[1]

Abstract

Background Minimal hepatic encephalopathy (MHE) is one of the most debilitating complications of hepatic cirrhosis, and visual electrophysiology, visual evoked potential (VEP) has long been used for MHE diagnosis. This technique only produces a summed response that is greatly dominated by the macular region. Multifocal visual evoked potential (mfVEP) imaging minimizes these limitations because it allows topographic recording of the optic nerve and visual cortex. The aim of this study was to detect minimal hepatic encephalopathy among cirrhotic patients using the mfVEP in comparison to the validated psychometric hepatic encephalopathy score (PHES), paired associative learning (PAL) and the Benton visual retention test (BVRT).

Methods Forty-five patients with compensated hepatic cirrhosis were enrolled in our study and compared to 45 normal controls who were matched for age, sex and educational level. Both groups underwent psychological tests (PHES, PAL, BVRT) and neurophysiological tests (mfVEP).

Results **1**According to the validated PHES, 14 patients were found to have MHE, 15 patients were found to have abnormal mfVEP, and abnormalities in the BVRT and PAL were found in 11 and 10 patients, respectively. **2-**mfVEP showed the highest sensitivity in the detection of MHE in reference to the PHES. **3-** The mfVEP test and potentially the BVRT have the advantage of detecting subtle abnormalities in non-MHE cirrhotic patients, for further research and follow-up are needed.

Conclusion mfVEP demonstates promising results for objective early detection of MHE, with a sensitivity of approximately 92.9%.

Keywords Multifocal visual evoked potentials, Hepatic cirrhosis, Minimal hepatic encephalopathy, Psychometric hepatic encephalopathy score

*Correspondence:
Reem M. Sabry
doctor_neurophysiology@med.bsu.edu.eg
[1]Department of Clinical Neurophysiology (Neuro-Diagnostic and Research Center), Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt
[2]Department of Gastroenterology, Hepatology and Infectious Diseases (Tropical Medicine department), Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt
[3]Department of Ophthalmology, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

Introduction

Hepatic encephalopathy (HE) is one of the critical complications of liver cirrhosis. It is a clinical syndrome with a wide range of variability, ranging from minimal impairments of intellectual function detectable only by specific psychometric testing (termed minimal hepatic encephalopathy [MHE]) to obvious neuropsychiatric abnormalities (termed overt hepatic encephalopathy [OHE]) [1].

MHE is one of the most debilitating complications, and it affects the quality of life of patients in addition to increasing the socioeconomic burden on family members and caregivers. MHE patients are at greater risk of occupational hazards, especially manual workers and drivers, and they endanger themselves and others, which is why early detection of MHE is necessary [2].

The psychometric hepatic encephalopathy score (PHES) battery assesses most MHE-related neuropsychological impairments; it assesses motor speed and accuracy, visual perception, visuospatial orientation, visual construction, concentration, attention, and (to a lesser extent) memory [3]. It was recommended for the diagnosis of MHE at the 11th World Congress of Gastroenterology, Vienna, 1998 [4].

Neurophysiological tools (EEG and evoked potentials) reflect changes in signal transmission in cortical networks. Neuronal electrogenesis depends on neuronal activity, which is influenced by the energy provided by the metabolic system and is sensitive to electrolyte homoeostasis and the clearance of toxic substances [5]. Therefore, clinical neurophysiology has been used for quantitative functional assessment and follow-up of metabolic encephalopathies [6].

Many previous studies have investigated the role of visual evoked potentials (VEPs), somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs) and electroencephalogram (EEG) signals in the diagnosis of MHE. (7–8).

The multifocal visual-evoked potential (mfVEP) technique has been developed to examine conduction in the parts of the visual field that conventional VEPs cannot assess. The mfVEP technique has a relatively high spatial resolution, allowing independent assessments of multiple regions [9].

Conventional pattern-reversal visual evoked potentials (PVEPs) only collect responses from the 8–10 central degrees of the visual field [10]. The mfVEP responses are extracted from the 40 to 50° radius of the visual field so that a broader range of optic damage can be detected than with conventional VEP [11].

Moreover, the mfVEP can estimate local defects without summing the responses from abnormal and normal regions such as the VEP [9].

To the best of our knowledge, no previous studies have investigated the role of mfVEP in the detection of MHE. Therefore, we designed this case–control study to clarify the effect of hepatic cirrhosis on the cerebral cortex and subcortical pathways using mfVEP and to elucidate the possibility of using multifocal visual evoked potentials (mfVEPs) for early detection of MHE among patients with compensated liver cirrhosis compared to the validated psychometric testing PHES.

Methods

Study design and participants

This case–control study was carried out at Beni-Suef University Hospital between October 2021 and April 2023. The study protocol was approved by the local ethical council of Beni-Suef University's Faculty of Medicine, and all subjects provided informed written consent prior to inclusion in the study.

Ninety patients were enrolled in this study and divided into two groups (patients and controls).

Based on clinical assessment, biochemical liver profile, and abdominal ultrasonography, 45 individuals were diagnosed with post hepatitis C liver cirrhosis. Patients were recruited from the hepatology outpatient clinic and the GIT Endoscopy section at Beni-Suef University hospitals.

All cirrhotic patients were compensated according to their Child–Pugh score (patients with maintained liver function but no ascites or symptomatic hepatic encephalopathy) [12]. The control group consisted of 45 healthy volunteers who were age-, sex- and education level-matched to the patients.

The following patient categories were excluded 1- patients with overt hepatic encephalopathy, 2- patients suffering from alcoholism, 3- patients suffering from neurological illnesses affecting cognition, such as Parkinsonism or dementia. 4- Patients with other end-of-life organ failure, such as renal, cardiac, or respiratory failure. 5 People who have hypernatremia or hypoglycemia 6-Patients younger than 18 years old 7-Patients with ocular illnesses that may impair visual function (e.g., lenticular or corneal opacities, glaucoma, uncorrected refraction errors, or diseases affecting gaze fixation) or a history of ocular trauma or surgery 8-Patients with systemic or metabolic illnesses known to impair vision (for example, cerebrovascular disease or diabetes mellitus). 9- Patients who were taking psychoactive drugs or who had a history of drug misuse, as well as those who had been exposed to toxic compounds, heavy metals, or any substance known to impair eyesight.

Clinical assessment

Patients were subjected to the following procedures:

(1) Clinical evaluation included a thorough history and physical examination, with a focus on the symptoms of chronic liver disease.
(2) CBC, ESR, urine analysis, liver function tests, kidney function tests, hepatitis markers, thyroid profile, serum electrolytes, alpha-fetoprotein (AFP), and HCV RNA PCR. The Child–Pugh score was calculated based on clinical and laboratory characteristics.
(3) Ultrasonography of the abdomen was used to confirm the presence of cirrhosis. The nodular liver surface, round edge, and parenchymal nodularity were all distinguishing features. Splenomegaly, ascites, and portosystemic collaterals could also be detected. Doppler ultrasound was performed on the hepatic and portal veins, as well as the hepatic artery and intra-abdominal portosystemic collaterals.
(4) Ophthalmological evaluation. A detailed history was collected to rule out any ocular, neurological, or systemic conditions that could impair vision. Visual acuity testing. Ophthalmological examination was performed to rule out any problems with the anterior or posterior segments.
(5) Cognitive evaluation

A. Psychometric Hepatic Encephalopathy Scale (PHES) was used to evaluate cognitive skills: ThePHES is a battery composed of five psychometric tests: the I-Number Connection Test (NCT-A)-IINumber Connection Test (NCT-B)-III-Digit Symbol Test (DST)-VI-Line Tracking Test (LTT)-V-Serial Dotting Test (SDT). The current definition of MHE is based on psychometric test scores that are two standard deviations above normal on at least two test
B. Paired Associate Learning Test (PALT) was used to assess auditory verbal memory. The test uses the concept of semantic cueing [14].
C. Benton visual retention test (BVRT): This test was used to assess visual perceptual, visual memory, visual motor and visuoconstructive abilities [15].

(6) Neurophysiological evaluation (multifocal visual evoked potential (mfVEP) test): The tests were performed at the Neurodiagnostic Research Centre (NDRC), Beni-Suef University Hospital, with a RetiScan 21 (Roland Consult, Brandenburg a.d. Havel, Germany) Roland RETI system (Roland, Germany).

All of the psychological and neurophysiological tests were performed within the same session

For mfVEP recording, gold cup electrodes filled with conducting cream were utilized, with a specific bridge connecting the electrodes to the head box. To achieve adequate cleaning, the skin is prepped using an abrasive gel (Nuprep). In all cases, the electrode impedance was kept below 5k.

For recording, four channels were used. A ground electrode on the forehead was used. Electrodes were implanted on the back of the skull in the following locations: one on the inion, another 4 cm above the inion, 4 cm to the left and 1 cm above the inion, and 4 cm to the right and 1 cm above the inion [16].

For stimulation, a cortically scaled dartboard stimulus with 60 segments (eccentricity up to 24 degrees), each with 16 checks (eight white and eight black), was employed, with a central 1-degree fixation target used as the fixing point.

Each segment had a 4 × 4 black and white grid that reversed patterns in a pseudorandom order. The computer screen's average background luminance was 73.5 cd/m2.

The stimulus was shown on a 20-inch monochrome monitor. The black and white checks quickly and regularly change phase (i.e., black to white and white to black). The viewing angle was 31 degrees. Vision correction was carried out when needed. A valid examination required an artifact level of less than 10% of the trials.

Each eye was tested individually, beginning with the right eye. Each eye received an average of 8 cycles, with each cycle consisting of 1000 responses and lasting 2.14 min.

Data analysis

The reposne consisted of 60 cortically scaled responses, and for each segment, the latecy and amplitude of P1 were calculated. An abnormal mfVEP response was defined as three contiguous segments in the same hemifield with p values less than 0.05 and at least one segment with a p value less than 0.02 (for both latency and amplitude). This is referred to as the cluster criterion (17–18). Segments with a statistically significant p value (< 0.05) for latency and/or amplitude were considered abnormal.

Ethical statement

The study was approved by the Faculty of Medicine, Beni-Suef University Research Ethics Committee (FM BSU REC) (FWA00015574 Approval number 30042019). Informed written consent was obtained from the participants.

Statistical Data Analysis

- The collected data were analyzed using SPSS for Windows, version 23.
- Continuous variables are presented as the mean ± standard deviation (SD), and categorical variables are presented as percentages.

Table 1 Comparison between cases and controls regarding the psychometric tests

Tests (mean ± SD)	Cases (no = 45)	Controls (no = 45)	*P* value
PAL	17.3 ± 3.5	19.4 ± 0.9	< 0.001*
BVRT error score (shapes)	20.1 ± 4.1	23.5 ± 0.9	< 0.001*
BVRTcorrect score (cards)	6.5 ± 2.3	8.8 ± 0.7	< 0.001*
NCT A (sec)	98.5 ± 53	41.4 ± 10.9	< 0.001*
NCT B (sec)	133.9 ± 56	75.1 ± 17.3	< 0.001*
DST (box)	25.6 ± 10.4	43.5 ± 9.9	< 0.001*
SDT (sec)	66.6 ± 21.1	50.1 ± 8.7	< 0.001*
LTT w (points)	86.9 ± 32.5	68.5 ± 13.9	0.001*

*P value is significant

[1]PAL: paired associate learning

[2]BVRT: Benton visual retention test (error score)

[3]BVRT: Benton visual retention test (correct score)

[4]NCT A: number connection test a

[5]NCT B: number connection test b

[6]DST: Digit Symbol Test

[7]SDT: Serial Dotting Test

[8]LTT w: Line Tracking Test (weighted score)

Table 2 Comparison between patients and controls regarding their multifocal VEP sum latency and amplitude

mfVEP sum (mean ± SD)	Cases (no = 45)	Controls (no = 45)	*P* value
Rt latency (msec)	141.9 ± 13.2	128.9 ± 8.9	< 0.001*
Lt latency	142.1 ± 13.2	129.1 ± 9.5	< 0.001*
Rt amplitude (μv)	5.8 ± 2.2	8.1 ± 1.9	< 0.001*
Lt amplitude	5.9 ± 2.3	8 ± 1.9	< 0.001*

*P value is significant

mfVEP: multifocal visual evoked potentials, sum latency measured in milliseconds (msec), sum amplitude measured in microvolt (μv)

- The chi-square test and Fisher test were used for comparisons among qualitative data, for quantitative data, comparisons will be performed using an independent sample t test.
- For more statistical analysis, suitable statistical tests of significance were used.
- Statistical significance were considered at p values < 0.05.

Results

The mean age of the patients at baseline was 50.9 ± 7.3 years, whereas the mean age of the patients in the control group was 48.13 ± 6.5 years, there was no statistical significant diffeence regaridng age (P value 0.064).

There was no significant difference regarding sex or years of education (p values of 0.833 and 0.851, respectively).

Regarding pschometric testing (PHES and BVRT and PAL tests), all tests showed statistically significant differences between cirrhotic patients and controls (p value < 0.001) (Table 1).

I- neurophysiological data

Analysis of the mfVEP data has been described regarding the sum response (the sum curve of all segments) and individual segment assessment.

- For both eyes, the studied patients had a significantly greater delay in the sum latency and a lower sum amplitude of the mfVEP than did the studied controls (P value < 0.001) (Table 2).
- Regarding individual segment analysis, there were 10 segments that showed significant differences between patients and controls in latency. The segment numbers are (1-27-32-35-41-52-56-57-58-59). Figure (1-A).

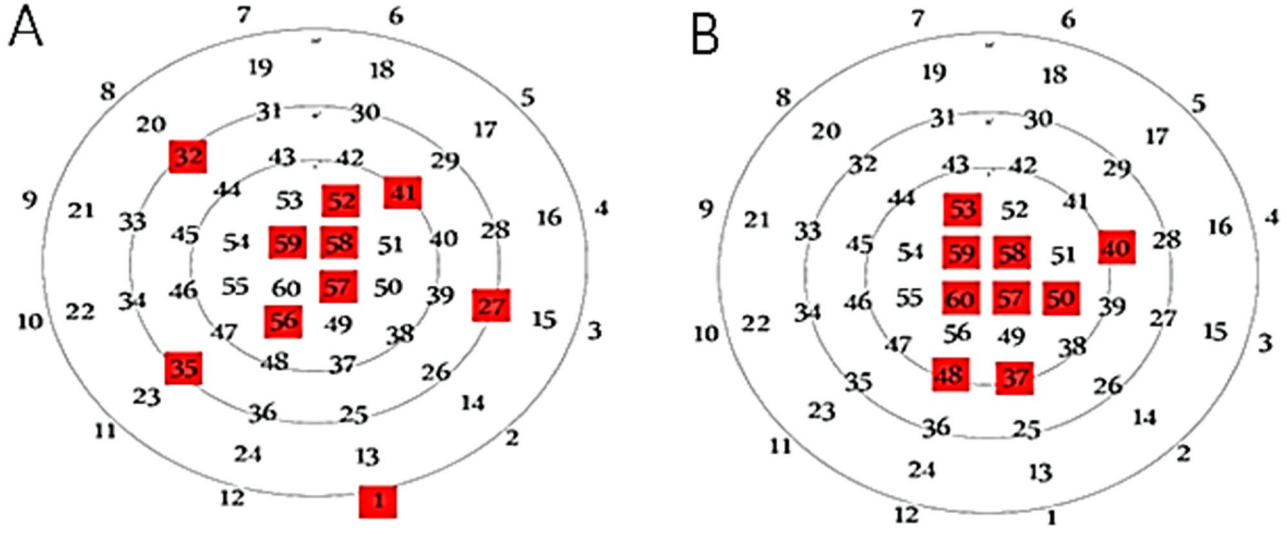

Fig. 1 shows the affected mfVEP segments in the cirrhotic group. **A**: Latency. **B**: amplitude

Table 3 Multiple linear regression analysis for formula calculation

Test	SD	Formula (regression equation) for normal patients
DST box	9.9	40.9-0.163×age + 0.812×years of education
NCT A sec	10.9	47.4 + 0.048×age-0.650×years of education
NCT B sec	17.3	81.9 + 0.328×age-1.8×years of education
SDT sec	8.7	37.4 + 0.391×age-0.486×years of education
LTTW	13.9	38.8 + 0.826×age-0.796×years of education

[1]DST: Digit Symbol Test

[2]NCT A: number connection test a

[3]NCT B: number connection test b

[4]SDT: Serial Dotting Test

[5]LTT w: Line Tracking Test (weighted score)

- There were 9 segments with significant differences in amplitude. The segment numbers are (37-40-48-50-53-57-58-59-60). Figure (1-B).

Prevalence of MHE among the patient group using the validated PHES.

The initial step was the identification of the variables that affected each PHES test. Variables that affected the outcomes of the PHES (age and educational level) were included in a multiple linear regression model. The results were used to construct distribution equations for each test according to the independent variables detected in relation to each of the tests and to age and years of schooling. (Table 3). Finally, we calculated the standard deviation (SD) for each test. This allowed us to construct normality tables for each psychometric test based on age and years of schooling [19].

The current definition of MHE is based on psychometric test results that are two SDs more than normal on at least two psychometric tests [13, 20].

The PHES is the sum of the scores of each test computed from the adjusted Z values according to the following formula: Z score = (measured value - expected value)/standard deviation [21].

According to the PHES results, 14 (31.1%) of the 45 cirrhotic patients were found to be positive for MHE. Versus 31 patients with negative results.

- According to the PHES, the patients were further subdivided into 2 subgroups according to the presence of MHE. The MHE group consisted of 14 patients, and the Non-MHE group consisted of 31 patients.
- Comparisons between these 2 abnormal subgroups and the control group were performed.

Comparisons between the MHE group and the non-MHE group vs. the control group

Regarding mfVEP

There was a significantly delayed latency and lower amplitude of the sum of the mfVEP on both sides between MHE patients and non-MHE patients, as shown in Table 4, and both groups showed significant differences in latency and amplitude compared to those of normal controls.

B-Regarding psychometric testing

The PAL score was significantly lower in MHE patients than in non-MHE patients and controls; however, there was no statistically significant difference in the PAL score between non-MHE patients and controls.

The Benton correct and error scores were significantly lower in the MHE group than in the non-MHE and control groups; furthermore, the non-MHE group had lower scores than the control group. As shown in Table 5.

II- sensitivity and specificity of different tests in the detection of MHE based on the PHES validated score using the ROC curve

As shown in Table 6, the multifocal VEP sum response and the Benton test had a significant role in the detection of MHE with high sensitivity and specificity.

Table 4 Comparison between patients and controls regarding their multifocal VEP sum latency and amplitude

mfVEP sum (mean ± SD)	Non MHE (no = 31)	MHE (no = 14)	Controls (no = 45)	P1-value Non-MHE vs. MHE	P2-value Non-MHE vs. Control	P3-value MHE vs. Control
Rt latency	134.8 ± 7.7	157.9 ± 7.3	128.9 ± 8.9	< 0.001*	0.011*	< 0.001*
Lt latency	134.9 ± 7.6	158.17.7	129.1 ± 9.5	< 0.001*	0.014*	< 0.001*
Rt amplitude	6.6 ± 1.9	4.1 ± 1.9	8.1 ± 1.9	< 0.001*	0.002*	< 0.001*
Lt amplitude	6.7 ± 1.9	4.2 ± 2	8 ± 1.9	< 0.001*	0.010*	< 0.001*

*P value is significant

mfVEP: multifocal visual evoked potentials, sum latency measured in milliseconds (msec), sum amplitude measured in microvolt (μv)

Table 5 Comparison between cases and controls regarding the psychometric tests

Tests (mean ± SD)	Non MHE (no = 31)	MHE (no = 14)	Controls (no = 45)	P1-value Non-MHE vs. MHE	P2-value Non-MHE vs. Control	P3-value MHE vs. Control
PAL	19.1 ± 0.8	13.4 ± 4.1	19.4 ± 0.9	< 0.001*	0.719	< 0.001*
BVRT error score (shapes)	22.2 ± 0.8	15.4 ± 4.7	23.5 ± 0.9	< 0.001*	0.016*	< 0.001*
BVRT correct score (cards)	7.7 ± 0.6	3.8 ± 2.3	8.8 ± 0.7	< 0.001*	< 0.001*	< 0.001*

*P value is significant

[1]PAL: paired associate learning

[2]BVRT: Benton visual retention test (error score)

[3]BVRT: Benton visual retention test (correct score)

Table 6 Sensitivity of the mfVEP, PAL and Benton tests in the detection of MHE

Parameters	MFVEP sum amp	MFVEP sum latency	PAL	BVRT shapes	BVRT cards
AUC	0.972	0.993	0.946	0.971	0.987
P value	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*
Cut off	≤ 5.6	> 142.9	≤ 14.5	≤ 20	≤ 6
Sensitivity	85.71(57.2–98.2)	92.86(66.1–99.8)	71.43(41.9–91.6)	78.57(49.2–95.3)	92.86(66.1–99.8)
Specificity	97.78(88.2–99.9)	100(92.1–100)	100(92.1–100)	97.78(88.2–99.9)	97.78(88.2–99.9)
PPV	92.3(63.1–98.8)	100(85–100)	100(92.1–100)	91.7(60.8–98.7)	92.9(65.1–98.9)
NPV	95.7(85.9–98.8)	97.8(87.2–99.7)	91.8(83.1–96.3)	93.6(84.3–97.6)	97.8(86.9–99.7)

*P value is significant

[1]PAL: paired associate learning

[2]BVRT: Benton visual retention test (error score) in shapes

[3]BVRT: Benton visual retention test (correct score) in cards

[4]AUC: area under the curve

[5]PPV: positive predictive value

[6]NPV negative predictive value

Table 7 Agreement between PHES and mfVEP in the detection of MHE

			PHES		Total
			Normal	Abnormal	
mfVEP	**NL**	Number	29	1	30
		% within mfVEP	96.7%	3.3%	100.0%
		% within PHES	93.5%	7.1%	66.7%
	Abn	Number	2	13	15
		% within mfVEP	13.3%	86.7%	100.0%
		% within PHES	6.5%	92.9%	33.3%
Total		Number	31	14	45
		% within mfVEP	68.9%	31.1%	100.0%
		% within PHES	100.0%	100.0%	100.0%
P value			< 0.001*		
Kappa agreement			0.91		
Overall agreement			93.3%		

*P value is significant

PHES: psychometric hepatic encephalopathy score

MfVEP: multifocal visual evoked potentials

III- agreement

Agreement between PHES and mfVEP in the detection of MHE

By applying the cluster criteria, 3 contiguous segments in the same hemifield had a ρ value less than 0.05, with at least one segment having a ρ value less than 0.02 (for both latency and amplitude) [17, 18, 22]. The cutoff values for the sum latency (> 142.9 msec) and sum amplitude (≤ 5.6 μv) were calculated.

Fifteen cirrhotic patients tested positive for mfVEP, 13 of whom were positive for MHE according to the PHES. Thirty cirrhotic patients were found to be normal by mfVEP (but one of them was abnormal by PHES).

All abnormal patients had delayed latencies; only 8 of them showed amplitudes smaller than the cutoff values in addition to their delayed latencies.

According to the kappa agreement test, there was significant strong agreement between the multifocal VEP and PHES in the detection of minimal hepatic encephalopathy (P value < 0.001), with an overall agreement of 93.3%., 92.9% sensitivity and 100% specificity (Table 7).

Agreement between the PHES and the PAL tests

The cutoff values for the PAL score were ≤ 14.5 points. Ten cirrhotic patients tested positive for PAL, all of whom were positive according to the PHES for MHE. Thirty-five cirrhotic patients were found to be normal by PAL (but 4 of them were abnormal by PHES).

Table 8 shows that there was significant strong agreement between the PAL test and PHES in the detection of minimal hepatic encephalopathy (P value < 0.001), with

Table 8 Agreement between the PHES and PAL tests for the detection of MHE

			PHES		Total
			Normal	Abnormal	
PAL (Cut off of abnormal values ≤ 14)	NL	Number	31	4	35
		% within PAL	88.6%	11.4%	100.0%
		% within PHES	100.0%	28.6%	77.78%
	Abn	Number	0	10	10
		% within PAL	0.0%	100.0%	100.0%
		% within PHES	0.0%	71.4%	22.22%
Total		Number	31	14	45
		% within PAL	68.9%	31.1%	100.0%
		% within PHES	100.0%	100.0%	100.0%
P value			0.001*		
Kappa agreement			0.91		
Overall agreement			91.1%		

*P value is significant

PHES: psychometric hepatic encephalopathy score

PAL: paired associate learning test

Table 9 Agreement between the PHES and the Benton test in the detection of MHE

			PHES		Total
			Normal	Abnormal	
BVRT	Normal	Number	31	3	34
		% within Benton	91.2%	8.8%	100.0%
		% within PHES	100.0%	21.4%	75.56%
	Abnormal	Number	0	11	11
		% within Benton	0.0%	100.0%	100.0%
		% within PHES	0.0%	78.6%	24.4%
Total		Number	31	14	45
		% within Benton	68.9%	31.1%	100.0%
		% within PHES	100.0%	100.0%	100.0%
P value			0.001*		
Kappa agreement			0.94		
Overall agreement			93.9%		

*P value is significant

PHES: psychometric hepatic encephalopathy score

BVRT: Benton visual retention test

an overall agreement of 91.1%, a sensitivity of 71.4%, and a specificity of 100.

Agreement between the PHES and the Benton test

The cutoff values for the Benton correct score ≤ 6 points and the error score ≤ **20** points were calculated. Eleven cirrhotic patients tested positive, all of whom were positive for MHE according to the PHES. Thirty-four cirrhotic patients were found to have normal Benton correction scores (3 of whom had abnormal PHES scores).

Table 9 shows that there was significant strong agreement between the Benton test and PHES in the detection of minimal hepatic encephalopathy (P value < 0.001), with an overall agreement of 93.9%, a sensitivity of 78.6% and a specificity of 100%.

Table 10 Detection of MHE by different tests

	PHES validated score	mfVEP	Benton	PAL
MHE	14	15	11	10
Non-MHE	31	30	34	35

[1]PHES: psychometric hepatic encephalopathy score

[2]PAL: paired associate learning test

[3]BVRT: Benton visual retention test

[4]mfVEP: multifocal visual evoked potentials

[5]MHE: hepatic patients having minimal hepatic encephalopathy

[6]Non-MHE: hepatic patients not having minimal hepatic encephalopathy

Total detection of MHE by all tests

The validated PHES score predicted 14 patients to have MHE in the cirrhotic group. The mfVEP was able to predict 15 patients, followed by the Benton test in 11 abnormal patients and then the PAL in 10 abnormal patients. (Table 10)

Discussion

Prevention of MHE is critical because of three factors. First, MHE may increase the likelihood of a traffic or labor accident. Second, it may have a negative impact on patient quality of life. Finally, MHE may be a predictor of future bouts of OHE [23].

In this study, we evaluated the mfVEP and compared its sensitivity to that of psychometric tests for detecting MHE. We examined 45 individuals with compensated hepatic cirrhosis, matched with 45 healthy controls based on age, sex, and education. Both groups were subjected to the following tests: PHES score, psychometric evaluations (PAL and BVRT) and mfVEP.

All five psychometric tests (PHES) revealed a substantial difference between cirrhotic patients and controls. According to the PHES, 14 patients (31.1%) were diagnosed with MHE. Previous studies have reported MHE prevalence among cirrhotics ranging from 30 to 84%, depending on the type of patient, technique, control group, and degree of liver disease [24–26]. Our patients were all compensated cirrhotics (child A), which explains their relatively low MHE incidence.

Based on our PHES results, the cirrhotic patients (45 patients) were further categorized into two groups: the MHE group (14 patients) and the non-MHE group (31 patients). In all subsequent tests, both categories were compared to those of the controls.

The PAL and BVRT scores were significantly different between cirrhotic patients and healthy controls. According to our predetermined cutoff, 11 patients had abnormal BVRT results, and 10 patients had abnormal PAL results.

Both tests revealed a significant difference between the MHE and control groups. Only the BVRT test showed a significant difference between non-MHE patients and controls. Denoting that short-term figural memory tests

are highly sensitive for detecting many types of cognitive deficiencies, they are particularly useful for evaluating patients with brain damage or disease [27, 28].

According to our estimated cutoff, 15 individuals were found to have abnormal mfVEP (all abnormal patients exhibited latency abnormalities, with only 8 patients having small amplitudes) [7, 8]. Few studies have gone beyond the temporal domain to find amplitude reduction [29, 30].

These abnormalities have been linked to encephalopathic changes related to cirrhosis. The fundamental cortical pathology is demyelination, which leads to axonal loss and fiber malfunction, resulting in low amplitude. Furthermore, in cirrhotic patients without MHE, these findings could be an early indicator of occipital brain demyelination [31].

Regarding the sum mfVEP response, significant differences were observed between cirrhotic patients and healthy controls in both latency and amplitude. Both MHE and non-MHE patients exhibited significantly delayed and smaller sum responses compared to healthy controls, with MHE patients showing more pronounced changes.

mfVEP Segment analysis revealed that significant differences in latency or amplitude between cirrhotic patients and healthy controls primarily located in the central part of the visual field. This findings is consistent with our previous work in which we tested compensated cirrhotic patients with PVEP (using 2 different check sizes) as the smaller checks that primary testing the central visual field, showed the most significant abnormalities, indicated that the central visual field was more affected than the peripheral [32]. These findings may also correlate with the loss of macular reflexes seen in hepatic retinopathy, first reported by Eckstein et al. [33].

Delayed latencies in mfVEP suggest demyelinating pathology, consistent with early neurophysiological markers of MHE (focal edema and myelin fiber dysfunction) [6, 34]. Amplitude reductions in evoked potentials likely reflect decreased number and synchronization of activated neurons in certain cortical regions, contributing to cortical dysfunction in cirrhosis [6].

Functional imaging studies corroborate this, showing the MHE -related brain anatomical and functional affection, such as decreased glucose absorption, cerebral oxygenation and cerebral blood flow [35–37], neuronal enlargement, interstitial edema, and aberrant metabolism in linked brain areas [38, 39]. Other studies showed impaired connectivity in cortical visual and associative areas such as the cuneus, precuneus, and middle temporal area V5 in MHE patients denoting impairment in visual, motion and spatial processing [40–42].

Our results indicate that mfVEP can detect preclinical neurodegenerative changes in cirrhotic patients classified as non-MHE by conventional psychometrics, revealing subclinical visual pathway impairment [43]. This aligns with studies showing similar neurophysiological abnormalities in non-MHE patients, suggesting a need to improve selectivity of the tests to detect even the smallest alteration and early monitoring of the cognitive functions of cirrhotic patients [44–46].

Comparative test analysis showed strong agreement between mfVEP and PHES in MHE detection, with mfVEP demonstrating 92.9% sensitivity and 93.5% specificity and potentially identifying subtle abnormalities that could be missed by PHES.

Similarly, the BVRT showed strong agreement with PHES, supporting its utility in detecting visuospatial and memory dysfunction in MHE [45, 46].

In conclusion, the mfVEP demonstrated high sensitivity for detection of MHE while showing a strong agreement with the validated PHES.

Conclusion

Cognitive effects in patients with MHE have been largely acknowledged [47, 48]; however, well-known practical diagnoses based on neuropsychological cognitive tests are easily limited by gender, age, education level or bias of test repeatability and illiteracy. mfVEP provides an objective method of detection of MHE beyond the traditional psychometrics, adding a sensitivity in detecting MHE.

We propose that combining mfVEP with the PHES could help early detection of MHE by identifying the subtle changes, potentially help prevention of more serious complications.

Abbreviations

BAEPs	Brainstem auditory evoked potentials
BVRT	Benton visual retention test
DST	Digit Symbol Test
EEG	Electroencephalogram
LTT	Line Tracking Test
mfVEP	Multifocal visual evoked potentials
MHE	Minimal hepatic encephalopathy
NCT A	Number connection test a
NCT B	Number connection test b
OHE	Overt hepatic encephalopathy
PALT	Paired associate learning test
PHES	Psychometric hepatic encephalopathy score
PRVEP	Pattern reversal visual evoked potentials (VEPs)
SDT	Serial Dotting Test
SSEPs	Somatosensory evoked potentials

Acknowledgements

We would like to thank the late esteemed Prof.Dr. Obsis Ibrahim Madkour, MD. Professor of neurology in Kasr Elainy faculty of medicine, Egypt, for her mentorship and support. We also would like to extent our deepest gratitude to the ROLAND CONSULT team of experts, Mr. Oscar Stasche, Mr. Joachim Finger and Mr. Uwe Held that provided invaluable assistance through the course of the study. Our sincere appreciation for Dr. Doaa Mahmoud Khalil MD lecturer of community medicine, faculty of medicine, Beni-Suef university, Egypt, for data and statistical analysis.

Author contributions
R.M.S done the neurophysiological and psychometric tests, wrote the manuscript. H.H revised the neurophysiological and psychometric data, performed the neurological examination of patients and controls. O.H and R.A.E chose the cirrhotic patients, ordered and and reviewed their labs and US data. R A E helped in the manuscript writing. H E M K and SI M have done the opthalmological assessment of the patients and controls.

Funding
No funding.

Data availability
Data are available from the coresponding author upon reasonable request.

Declarations

Ethical approval
Ethical approval for this study was obtained from the Research ethical committee of Beni-Suef University. The ethical committee approval number was FWA00015574. The study was performed in agreement with the Declaration of Helsinki. All participates were evaluated and determined to be capable of providing informed consent for their participation in the study. Written informed consent was obtained from all participants prior to their inclusion in the study. FM BSU REC is organised and operated ccording to guidelines of the declaration of Helenski, Interntional Conference of Harmonization (ICH) and united states codes of federal regultions and registered in under the fedral wide assurance for the protection of the human subjects.

Consent to publication
Not applicable. As the manuscript doesn't include any identifying images, personal or clinical details of the participant, only anonymized numerical data are presented.

Competing interests
The authors declare no competing interests.

Received: 28 April 2024 / Accepted: 10 January 2025
Published online: 04 February 2025

References

1. Butterworth RF, McPhail MJW. (2019): L-ornithine L-aspartate (LOLA) for hepatic encephalopathy in cirrhosis: Results of randomized controlled trials and meta-analyses. Drugs; 79 (1): 31–37.
2. Ridolaa L, Cardinalea V, Riggio O. The burden of minimal hepatic encephalopathy: from diagnosis to therapeutic strategies. Annals Gastroenterol. 2018;31:151–64.
3. Seo YS, Yim SY, Jung JY, Kim CH, Kim JD, Keum B, An H, Yim HJ, Lee HS, Kim CD, Ryu HS, Um SH. Psychometric hepatic Encephalopathy score for the detection of minimal hepatic encephalopathy in Korean patients with liver cirrhosis. J Gastroenterol Hepatol. 2012;27:1695–704.
4. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy: definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congress of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716–21.
5. Formentin C, Zarantonello L, Mangini C, Frigo AC, Montagnese S, Merkel C. Clinical, neuropsychological and neurophysiological indices and predictors of hepatic encephalopathy (HE). Liver Int. 2021;41:1070–82.
6. Amodio P, Montagnese S. Clinical neurophysiology of hepatic encephalopathy. J Clin Experimental Hepatol. 2015;5(1):60–8.
7. Zhang L, Li L, Zhou X, Xia F, Zhang Z. Visual electrophysiological examination in diagnosis of hepatic encephalopathy. World J Neurosci. 2013;3:204–8.
8. El-Sherif AM, Abdelrazik FG, Helal AE, Essmet A, Abdelsayed AM, Abdelsayed MM. Diagnosis of minimal hepatic encephalopathy of cirrhotic patients using a combination of neuropsychiatric and neurophysiological tests. Egypt J Hosp Med. 2018;73(4):6541–54.
9. El Habashy HR, El Gohary AM, Azmy RM, Hegazy MI, Elsanabary ZS, Tawfeek AA. Multifocal visual evoked potential in idiopathic intracranial hypertension. Egypt J Neurol Psychiat Neurosurg. 2014;51(4):477–82.
10. Jancic J, Ivančević N, Nikolić B, Popović M, Martinović Z, Stevanović D, Grbić M, Đurić V, Samardžić J. (2016): Visual evoked potentials current concepts and future perspectives. Vojnosanitetski pregled (military-medical and pharmaceutical review); 75:342–2. https://doi.org/10.2298/VSP160613342J
11. Park S, Park SH, Chang JH, Ohn YH. Study for analysis of the multifocal visual evoked potential. Korean J Ophthalmol. 2011;25(5):334–40.
12. Andres R, Melisa D, Richard F. From child–Pugh to MELD score and beyond: taking a walk down memory lane. Ann Hepatol. 2021;27:100535. https://doi.org/10.1016/j.aohep.2021.100535.
13. Wang JY, Zhang NP, Chi BR, YQi M, Liu MLN, Wang YD, Jiang JB, Yang HX, Xu JH, Li Y, Xu X, Zhang JM, Zhou G, Zhuge XM, Tian YZ, Ye DA, Liu J YL. Prevalence of minimal hepatic encephalopathy and quality of life evaluations in hospitalized cirrhotic patients in China. World J Gastroenterol. 2013;19(30):4984–91.
14. Scorpio KA, Islam R, Kim SM, Bind R, Borod JC, Bender HA. Paired-associate learning. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of clinical neuropsychology. Cham: Springer; 2018. https://doi.org/10.1007/978-3-319-57111-9_1137.
15. Manna CG, Alterescu K, Borod JC, Bender HA. Benton Visual Retention Test. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of clinical neuropsychology. New York, NY: Springer; 2011. https://doi.org/10.1007/978-0-387-79948-3_1110.
16. Wolff BE, Bearse MA, Schneck ME, Barez S, Adams AJ. Multifocal VEP (mfVEP) reveals abnormal neuronal delays in diabetes. Doc Ophthalmol Adv Ophthalmol. 2010;121:189–96.
17. Zafeiropoulos P, Katsanos A, Kitsos G, Stefaniotou M, Asproudis I. The contribution of multifocal visual evoked potentials in patients with optic neuritis and multiple sclerosis:a review. Doc Ophthalmol. 2021;142:283–92.
18. De Moraes CGV, Liebmann JM, Ritch R, Hood DC. Understanding disparities among Diagnostic technologies in Glaucoma. Arch Ophthalmol. 2012;130(7):833–40.
19. Padilla Ruiz MA. Cuban normality tables for psychometric tests used for diagnosis of minimal hepatic encephalopathy. Colombian J Gastroenterol. 2016;31(3):216–22.
20. Wang JY, Zhang NP, Chi BR, YQi M, Liu MLN, Wang YD, Jiang JB, Yang HX, Xu JH, Li Y, Xu X, Zhang JM, Zhou G, Zhuge XM, Tian YZ, Ye DA, Liu J YL, Kumaravel G. Kumaravel, G. (2015): Psychometric hepatic encephalopathy score for the detection of minimal hepatic encephalopathy in South Indian patients with liver cirrhosis (Doctoral dissertation, Madras Medical College, Chennai).
21. -Amodio P, Campagna F, Olianas S, Iannizzi P, Mapelli D, Penzo M, Angeli P, Gatta A. Detection of minimal hepatic encephalopathy: normalization and optimization of the psychometric hepatic encephalopathy score. A neuropsychological and quantified EEG study. J Hepatol. 2008;49:346–53.
22. -Klistorner A, Fraser C, Garrick R, Graham S, Arvind H. Correlation between full-field and multifocal VEPs in optic neuritis. Doc Ophthalmol. 2008;116:19–27.
23. -Flud CR, Duarte-Rojo A. Prognostic implications of Minimal/Covert hepatic encephalopathy: large-scale validation cohort studies. J Clin Experimental Hepatol. 2019;9(1):112–6.
24. -Srivastava A, Chaturvedi S, Gupta RK, Malik R, Mathias A, Jagannathan NR, Jain S, Pandey CM, Yachha SK, Rathore RKS. Minimal hepatic encephalopathy in children with chronic liver disease: prevalence, pathogenesis and magnetic resonance-based diagnosis. J Hepatol. 2017;66:528–36.
25. -Abdelrahman ME, Mahmouda SZ, Ali AM, Ahmed H, El-Khateeb AT, Mohamed GA. Screening for minimal hepatic encephalopathy among asymptomatic drivers with chronic liver disease. Egypt J Intern Med. 2018;30:217–22.
26. -Bale A, Pai CG, Shetty S, Balaraju G, Shetty A. Prevalence and factors Associated with minimal hepatic encephalopathy in patients with cirrhosis of liver. J Clin Experimental Hepatol. 2018;8(2):156–61.
27. Vannest J, Szaflarski JP, Privitera MD, ScheffTbk, Holland SK. Medial temporal fMRI activation reflects memory lateralization and memory performance in patients with epilepsy. Epilepsy Behav. 2008;12:410–8.
28. Thompson SB, Gander J. Immediate Memory Functioning and Intelligence quotients of 18–30 years Age Group using New Data Derived from the Benton Visual Retention Test: Applicability to alzheimers Disease patients. Geriatric Med. 2011;2(3):WMC001652.
29. Zamir D, Storch S, Kovach I, Storch R, Zamir C. Early detection of hepatic encephalopathy by recording visual evoked potential (VEP). Rocz Akad Med Bialymst. 2002;47:186–93.
30. Ryu N, Gao W, Yan M. Evaluation of brain evoked potentials in the detection of subclinical hepatic encephalopathy in cirrhotics. Bain Nerve. 1997;49(10):887–92. Abstract (Article in Japanese).

31. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic Encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol. 2001;96(9):2718–23.
32. Elfatah RMSA, Soliman HH, Hammad OM, Khalil HEM, Mohammed SI, Eid RA. Different check sizes pattern-reversal visual evoked potentials study in patients with compensated hepatic cirrhosis. Int J Health Sci. 2022;6(S4):8129–39. https://doi.org/10.53730/ijhs.v6nS4.11780.
33. Eckstein AK, Reichenbach A, Jacobi P, Weber P, Gregor M, Zrenner E. Hepatic retinopathia. Changes in retinal function. Vis Res. 1997;37:1699–706.
34. Hood DC, Chen JY, Yang EB, Rodarte C, Wenick AS, Grippo TM, Odel JG, Ritch R. The role of the multifocal visual evoked potential(mfVEP) latency in understanding optic nerve and retinal diseases. Trans Am Ophthalmol Soc. 2006;104:71–7.
35. Qi R, Zhang LJ, Xu Q, Zhong J, Wu S, Zhang Z, Liao W, Ni L, Zhang Z, Chen H, Zhong Y, Jiao Q, Wu X, Fan X, Liu Y, Lu G. (2012): Selective impairments of resting-state networks in minimal hepatic encephalopathy. PLoS One. 2012;7(5):e37400.
36. Chen LH, Shi JY, Zou TX, Zhang L, Gou YP, Lin YQ, Chen HJ. Disturbance of thalamic metabolism and its association with regional neural dysfunction and cognitive impairment in minimal hepatic encephalopathy. Eur J Radiol. 2020;131:109252.
37. Zhan CY, Chen HJ, Gao YQ, Zou TX. Functional Network-based statistics reveal abnormal resting-state functional connectivity in minimal hepatic encephalopathy. Front Neurol. 2019. https://doi.org/10.3389/fneur.2019.00033. 10,10.
38. Zhong WJ, Zhou ZM, Zhao JN, WuW, Guo DJ. Abnormal spontaneous brain activity in minimal hepatic encephalopathy: resting-state fMRI study. Diagn Interv Radiol. 2016;22:196–200.
39. Goel A, Yadav S, Saraswat V, Srivastava A, Thomas MA, Pandey CM, Rathore R, Gupta R. Cerebral edema in minimal hepatic encephalopathy due to extrahepatic portal venous obstruction. Liver Int. 2010;30(8):1143–51.
40. Zafiris O, Kircheis G, Rood HA, Boers F, Haussinger D, Zilles K. Neuralmechanismunderlying impaired visual judgment in the dysmetabolic brain: an fMRI study. NeuroImage. 2004;22(2):541–52.
41. Sun Q, Fan WL, Ye J, Han P. Abnormal Regional Homogeneity and Functional Connectivity of Baseline Brain Activity in Hepatitis B Virus-related cirrhosis with and without minimal hepatic encephalopathy. Front Hum Neurosci. 2018;12:245. https://doi.org/10.3389/fnhum.2018.00245.
42. Cheng Y, Zhang G, Zhang X, Li Y, Li J, Zhou J, Huang L, Xie S, Shen W. Identification of minimal hepatic encephalopathy based on dynamic functional connectivity. Brain Imaging Behav. 2021. https://doi.org/10.1007/s11682-021-00468-x.
43. Cona G, Bisiacchi PS, Amodio P, Schiff S. Age-related decline in attentional shifting: evidence from ERPs. Neurosci Lett. 2013;556:129–34.
44. Bisiacchi P, Cona G, Tarantino V, Schiff S, Montagnese S, Amodio P, Capizzi G. Assessing inter- and intraindividual cognitive variability in patients at risk for cognitive impairment: the case of minimal hepatic encephalopathy. Metab Brain Dis. 2014;29:945–53.
45. Garcia-Garcia R, Cruz-Gómez AJ, Urios A, Mangas-Losada A, Forn A, Escudero-García D, Kosenko E, Torregrosa I, Tosca J, Giner-DuránR, Serra MA, AvilaC, Belloch V, Felipo V, Montoliu C. Learning and memory impairments in patients with minimal hepatic encephalopathy are Associated with Structural and functional connectivity alterations in Hippocampus. Sci Rep. 2018;8:9664–77.
46. Torres DS, Abrantes J, Brandão-Mello CE. Cognitive assessment of patients with minimal hepatic encephalopathy in Brazil. Metab Brain Dis. 2013;28:473–83.
47. Jiao Y, Wang XH, Chen R, Tang TY, Zhu XQ, Teng GJ. Predictive models of minimal hepatic encephalopathy for cirrhotic patients based on large-scale brain intrinsic connectivity networks. Sci Rep. 2017;7:11512. https://doi.org/10.1038/s41598-017-11196-y.
48. Damulin IV. Minimal hepatic encephalopathy: current clinical and pathogenetic aspects. Ter Arkh. 2018;90(2):89–93. (abstract, article in Russian).

Publisher's note