EncephalApp Stroop App predicts poor sleep quality in patients with minimal hepatic encephalopathy due to hepatitis B-induced liver cirrhosis

Ming Luo, Xiao-Bing Yu, Sheng-Juan Hu, Fei-Hu Bai

Department of Gastroenterology, Ningxia People's Hospital, 301 Zhengyuan North Street, Jinfeng District, Yinchuan, Ningxia, PR China

Abstract

Background/Aim: A novel computerised Stroop test- EncephalApp Stroop App (EncephalApp) has good diagnostic validity for minimal hepatic encephalopathy (MHE) in cirrhotic patients. The Stroop test is correlated with sleep disturbances which are common, and severely affects health-related quality of life in cirrhotic patients with MHE. We evaluated the relationship between sleep quality and EncephalApp results in patients with MHE due to hepatitis B-induced liver cirrhosis.

Patients and Methods: We enrolled 180 adult patients with hepatitis B-induced cirrhosis. All patients were tested using the psychometric hepatic encephalopathy score (PHES) and EncephalApp. We analysed the diagnostic validity of EncephalApp for MHE using PHES as the gold standard for reference. The sleep quality of included patients was evaluated using the Pittsburgh Sleep Quality Index (PSQI). The predictive factors for poor sleep quality were analysed using backwards conditional stepwise logistic regression analysis.

Results: Ninety-eight patients (54.4%) were diagnosed with MHE by PHES. Receiver operating characteristic (ROC) curve analysis showed that the threshold value of EncephalApp for MHE diagnosis was 225.60 s. EncephalApp showed 85.2% sensitivity and 77.3% specificity for diagnosing MHE; the area under the ROC curve was 0.864. PSQI scores of cirrhotic patients with MHE were significantly lower than those without MHE ($P < 0.05$). Child Turcotte Pugh grades (Odds ratio [OR] = 2.11 [1.55–2.85], $P < 0.01$) and the total Off-time plus On-time of EncephalApp (OR = 4.14 [1.95–6.29], $P < 0.01$) were independent predictors of poor sleep quality in MHE patients.

Conclusions: The total Off-time plus On-time of EncephalApp predicts poor sleep quality in patients with MHE due to hepatitis B-induced cirrhosis.

Keywords: EncephalApp Stroop App, minimal hepatic encephalopathy, sleep quality, Stroop test

Address for correspondence: Dr. Fei-Hu Bai, Department of Gastroenterology, Ningxia People's Hospital, 301 Zhengyuan North Street, Jinfeng District, Yinchuan, Ningxia 750021, PR China.
E-mail: baifeihu@hotmail.com

See accompanying Editorial

INTRODUCTION

Hepatic encephalopathy (HE) is a severe and frequent

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complication of decompensated cirrhosis and/or portosystemic shunting.[1] It is a reversible cerebral dysfunction with a broad range of clinically neurological and psychiatric defects, ranging from mild abnormalities to coma.[1] Based on the severity of clinical manifestation, HE is divided into two types: overt HE and covert HE.[1] Overt HE presents with obvious neuropsychiatric symptoms including asterixis, dyspraxia and even coma. By contrast, covert HE includes minimal HE (MHE) and WestHaven grade I HE. MHE presents trivial neuropsychiatric deficits identified by neurophysiological and psychometric tests in cirrhotic patients without a distinct clinical symptom of overt HE.[2] Epidemiological surveys showed that the prevalence of MHE varies between 30% and 70% among cirrhotic patients, in accordance with various diagnostic methods in different populations.[3-5] MHE impairs driving skills, affects health-related quality of life (QoL) and induces a high risk of progression to overt HE.[3,4,6,7]

Till date, there have been no universal and standard diagnostic tests to evaluate MHE in clinical practice. The updated guideline by the American Association for the Study of Liver Diseases (AASLD) recommends the psychometric hepatic encephalopathy score (PHES) for the diagnosis of MHE.[1] The Stroop test evaluates cognitive alertness and psychomotor speed by measuring the time required to correctly identify a series of printed words and symbols with different colours.[8] It has been successfully applied to assess neurocognitive deficits due to brain damage, Alzheimer's disease and Parkinson's disease.[9-11] Based on the paper-and-pencil Stroop test, Bajaj *et al*. developed an application of computerised Stroop test- EncephalApp Stroop App (EncephalApp), for diagnosing MHE in 2013.[12] EncephalApp is operated by the iPhone operating system (iOS) on the smartphone or computer, and it has been translated into several languages including English, German and Chinese. Recently, EncephalApp has been verified to be a rapid, effective and convenient approach for diagnosing MHE in clinical practice using the PHES as the gold standard for reference.[12-14]

Poor sleep quality is frequent among cirrhotic patients with MHE.[15] It severely affects health-related QoL and is associated with worse prognosis in these patients.[15,16] Early prediction of poor sleep quality in cirrhotic patients with MHE is critical for subsequent treatment and follow-up. The Stroop test results have been found to be correlated with sleep disorder and disturbances of the circadian rhythm, which induces poor sleep quality in healthy volunteers.[17,18] Nevertheless, the correlation between the results of EncephalApp, as a novel diagnostic method of MHE and poor sleep quality in MHE patients remains unclear. Therefore, the present study was aimed to analyse the correlation between EncephalApp results and poor sleep quality in these patients. We hypothesised that EncephalApp would predict poor sleep quality in patients with MHE due to hepatitis B-induced cirrhosis.

PATIENTS AND METHODS

Patients
In total, we included 250 patients with hepatitis B-induced cirrhosis, who were hospitalised in the Department of Gastroenterology of Ningxia People's Hospital between January 2016 and January 2019. Cirrhosis was diagnosed according to liver biopsy, ultrasound or radiological imaging, endoscopic features of portal hypertension and medical history. Exclusion criteria were as follows: clinical symptoms of overt HE; history of overt HE; history of recent alcohol abuse (<3 months); recent intake history of lactulose, probiotics, rifaximin or psychotropic drugs (<3 months); recent history of upper gastrointestinal haemorrhage, electrolyte disturbance or spontaneous bacterial peritonitis (<3 months); history of hepatocellular carcinoma or other malignancies; history of non-alcoholic fatty liver diseases; history of portosystemic shunt or transjugular intrahepatic portosystemic shunt; history of diagnosed sleep disorders and/or obstructive sleep apnea; neurological diseases including cerebral infarction, Parkinson's disease or Alzheimer's disease; serious organ dysfunction including renal failure, chronic obstructive pulmonary disease or heart failure and inability to perform the PHES and EncephalApp tests due to impaired vision or illiteracy. According to these exclusion criteria, 70 cirrhotic patients were excluded and 180 cirrhotic patients were included in this study [Figure 1]. The severity of cirrhosis was evaluated using the model of end-stage liver disease (MELD) score and Child-Turcotte-Pugh (CTP) grade.[19]

Diagnosis of MHE
As recommended in the updated guideline by the AASLD, the PHES was used to diagnose MHE in the included cirrhotic patients. The PHES consists of the number connection test-A (NCT-A), the number connection test-B (NCT-B), the digit symbol test (DST), the serial dotting test (SDT) and the line tracing test (LTT). As some of the included patients were unfamiliar with the English alphabets, the English alphabets were replaced with Chinese alphabets in NCT-B with the same sequence.[20] Under the one-on-one guidance of trained medical staff, the included cirrhotic patients underwent the PHES test in a quiet environment with adequate illumination. The subtests of the PHES were considered abnormal when
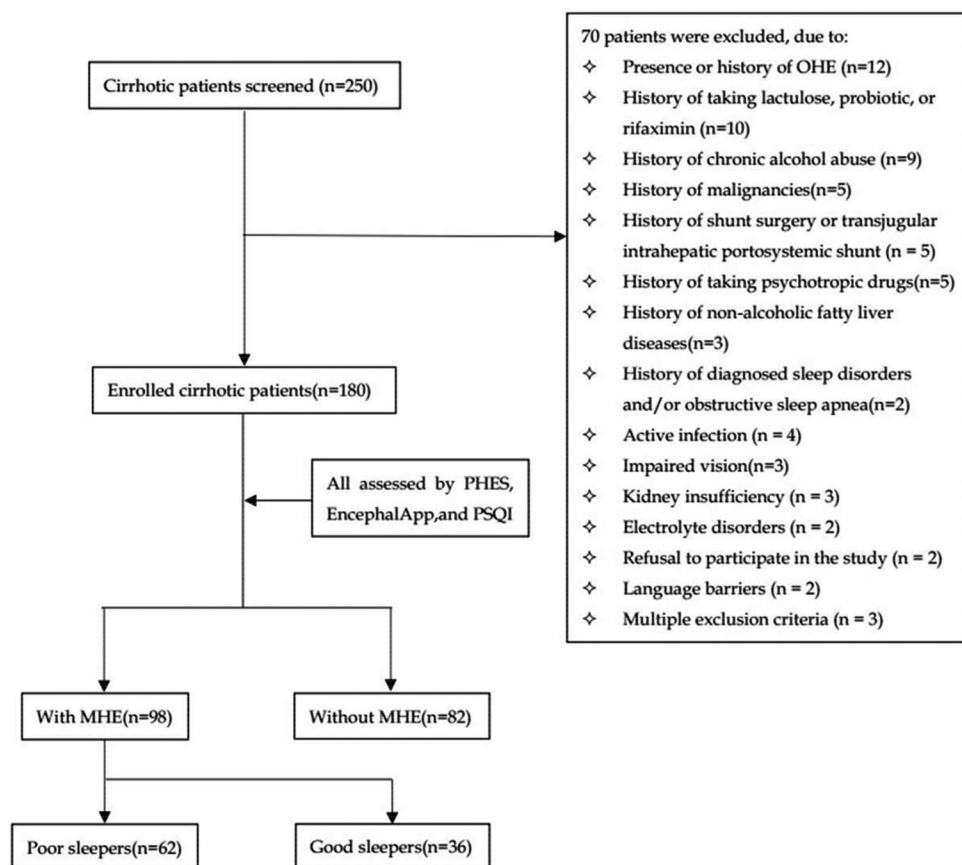
Figure 1: Flow diagram of cirrhotic patients enrolled in this study and the reasons for the dropout of screened patients. Psychometric Hepatic Encephalopathy Score (PHES), Pittsburgh Sleep Quality Index (PSQI)

the test score was more than mean ± 2 standard deviations from the age/education-matched controls.[20] When the PHES score was less than –4 points, cirrhotic patients were diagnosed with MHE.[20] For every included patient, 25 min were required to complete the PHES test.

After testing with PHES, included patients received the Stroop test using EncephalApp. EncephalApp was administered using the iPad Pro with a 10.5-inch screen. It consists of two components: an easy 'off' state and a difficult 'on' state. In the 'off' state, coloured signs ### are presented on the screen and participants are required to identify the corresponding colour. In the 'on' state, EncephalApp presents a discordant coloured word. EncephalApp has practice runs before the test runs, and the order of tests are as follows: (1) two practice 'off' runs, (2) five test 'off' runs, (3) two practice 'on' runs and (4) five test 'on' runs. In the 'off' and 'on' state, it requires participants to concentrate on the visual stimulus and choose the appropriate colour by pressing on the screen, and the response time is calculated using 'Off-time' and 'On-time'. It takes about 15 mins to complete all subtests of EncephalApp. The specific results of EncephalApp are as follows: (1) total time for five correct runs in the 'off'

state (Off-time); (2) number of runs required to finish the five correct 'off' runs; (3) total time for five correct runs in the 'on' state (On-time); and (4) number of runs required to finish the five correct 'on' runs. The Off-time plus On-time is used to distinguish cirrhotic patients with MHE from those without MHE.

Laboratory tests

On the same day of PHES and EncephalApp tests, venous blood samples of all included patients were collected after overnight fasting. These samples were sent for routine blood biochemistry tests, haematological parameters and viral tests. Blood biochemistry and plasma levels of ammonia (normal range: 5–35 mmol/L) were determined by the dry chemistry method, using the Vitros 350 Dry Chemistry System (Ortho Clinical Diagnostics, New Jersey, USA) within 20 min. Blood coagulation parameters were measured using the Beckman Coulter ACL 7000 Coagulation Analyzer (Beckman Coulter Diagnostics, Georgia, USA), and routine blood tests were performed by the Beckman Coulter LH 750 Haematology Analyser (Beckman Coulter Diagnostics, Georgia, USA). Serum levels of HBV-DNA (detection level: 12 IU/ml) were measured

using the Cobas TaqMan HBV-DNA qualitative test (Roche Diagnostics GmbH, Mannheim, Germany).

Evaluation of sleep quality

The Chinese version of the Pittsburgh Sleep Quality Index (PSQI) was used for evaluating the sleep quality of included cirrhotic patients. PSQI has been demonstrated to have good reliability and validity to evaluate sleep quality in China.[21] It contains seven sub-components including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. Each sub-component of the PSQI is scored between 0 and 3 and then all sub-component scores are summed to a global score between 0 and 21. It takes about 20 min to complete the questionnaire of the PSQI. Higher scores are suggestive of worse sleep quality. A global PSQI score >5 has been validated to be a reliable threshold value to distinguish between poor and good sleepers.[21,22]

Ethics

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki (6th revision, 2008) and was approved by the ethics committee. Written informed consent was obtained from all participants and their relatives before inclusion in the study.

Statistical analysis

Quantitative data are described as mean ± standard deviation or median with interquartile ranges (IQR), and the Student's *t*-test or Mann–Whitney U-test was applied for comparison. Categorical variables were respectively expressed as frequencies and percentages, and the Chi-square test and Fisher's exact test were used to compare differences between groups. The receiver operating characteristic (ROC) curves were used to determine the threshold value of EncephalApp for the diagnosis of MHE, and the area under the ROC curve higher than 0.7 was considered significant.

The correlation between parametric variables was assessed using the Pearson coefficient of correlation. By contrast, the Spearman coefficient of correlation was used to evaluate the correlation between non-parametric variables. Univariate analyses were applied to evaluate the difference concerning demographic variables, clinical profile, PHES results, EncephalApp results and sleep quality between cirrhotic patients with and without MHE. A backward conditional stepwise logistic regression analysis was applied to identify the independent predictors of poor sleep quality from candidate variables which were found to be significantly different

Table 1: Clinical and demographic characteristics of included cirrhotic patients

Variable	Data
Number of cirrhotic patients	180
Age (years)	56 (23-70)
Gender (male/female)	95/85
Education (years)	9 (5-20)
Body mass index (BMI)	20.4 (16.5-33.8)
Aetiology of cirrhosis	
Viral hepatitis B	100%
Child-Turcotte-Pugh grade (A/B/C)	153/23/4
MELD score	9.46±3.54
Previous hospitalisation	115 (64%)
A complication of cirrhosis	
Ascites	39 (22%)
Portal thrombosis	9 (5%)
Anaemia	30 (17%)
Thrombocytopenia	25 (14%)
Ammonia (µmol/L)	38.5±6.5
HBV treatment by nucleoside analogues	165 (92%)
Entecavir	132 (74%)
Tenofovir	33 (18%)
HBV-DNA (positive/negative)	115/65
Haemoglobin (g/L)	98±24
Serum sodium (mmol/L)	131±7.8
C-reactive protein (mg/L)	5.84±3.0
Creatinine (µmol/L)	56.3±20.1

Quantitative data are described as mean ± standard deviation or median with interquartile ranges, and categorical variables are expressed as frequencies with percentages

in univariate analyses. Multivariate odds ratios (OR) and 95% confidence intervals (CI) of the independent predictors were calculated simultaneously. Data were analysed using IBM SPSS Statistic Version 23.0 (IBM Corporation, New York, USA), and $P < 0.05$ was considered to be significant.

RESULTS

Baseline characteristics of included cirrhotic patients

Of the total 250 cirrhotic patients screened; eventually, 180 patients were included. More than half of the patients were men, with a median age of 56 years (range 23–70 years). The median education time was 9 years (range 5–20 years). The underlying aetiology of cirrhosis for all included patients was viral hepatitis B infection. Of these cirrhotic patients, 153 (85%), 23 (13%) and 4 (2%) patients were classified as CTP grades A, B and C, respectively. The median of the body mass index (BMI) in included patients was 20.4 (range 16.5–33.8). Ten patients were diagnosed as obese, on the basis of BMI of more than 30. Obese patients were diagnosed without obstructive sleep apnea after they were examined using sleep monitoring. Of these patients, 115 (64%) had histories of previous hospitalisation. A total of 165 (92%) patients had been treated with nucleoside analogues including entecavir and tenofovir, and the HBV-DNA of 115 (64%) patients were positive.

Table 2: Comparison of clinical and demographic characteristics between cirrhotic patients with and without MHE

Variable	MHE	Without MHE	t/χ^2	P
Number of patients	98	82		
Age (years)	58 (28-69)	54 (23-70)	-1.59	0.11
Gender (male/female)	52/46	43/39	0.01	0.93
Education (years)	9 (5-16)	9 (5-20)	0.75	0.46
Body mass index (BMI)	21.5 (16.5-32.2)	20.9 (17.2-33.8)	0.62	0.33
Child-Turcotte-Pugh grade (A/B/C)	77/18/3	76/5/1	7.76	0.02
MELD scores	9.46±3.54	7.03±4.32	-2.41	0.02
Ammonia (μmol/L)	56.8±7.52	25.5±5.53	21.1	<0.01
HBV-DNA (positive/negative)	60/38	55/27	1.33	0.25
Haemoglobin (g/L)	95±30	105±26	-0.24	0.81
Serum sodium (mmol/L)	130±7.42	133±8.52	1.69	0.09
C-reactive protein (mg/L)	6.01±3.22	5.23±2.54	-1.84	0.07
Creatinine (μmol/L)	58.4±21.2	55.8±19.4	-0.85	0.39
PHES results	-7.22±2.95	1.41±2.50	21.08	<0.01
Number connection test-A	81.3±20.8	56.6±18.6		
Number connection test-B	114.2±34.3	82.1±25.5		
Digit symbol test	24.09±9.22	35.8±8.80		
Serial dotting test	73.5±15.3	65.3±17.8		
Line tracing test	76.2±24.8	67.8±23.3		
EncephalApp results				
Total Off-time (s)	132.1±24.5	92.7±15.9	12.52	<0.01
Total On-time (s)	128.8±23.8	93.3±14.1	11.87	<0.01
Median trials for five off correct runs (range)	7 (6-19)	6 (5-17)	1.32	0.23
Median trials for five on correct runs (range)	7 (6-20)	6 (5-16)	2.34	0.45
Total On-time plus Off-time (s)	248.6±45.3	193.7±29.1	-9.46	<0.01
PQSI scores	14.5±4.05	9.60±3.05	-8.93	<0.01
Sleep quality	2.12±1.30	2.47±1.24	-3.31	<0.01
Sleep latency	2.20±1.22	1.30±1.10	-5.20	<0.01
Sleep duration	2.18±1.10	1.50±0.80	-4.66	0.03
Habitual sleep efficiency	2.10±0.90	1.90±0.62	-1.70	0.09
Sleep disturbances	2.50±1.20	1.83±0.72	-4.43	<0.01
Use of sleep medication	2.10±1.10	1.20±0.55	6.74	<0.01
Daytime dysfunction	2.56±1.45	1.80±0.85	-4.18	0.01

MHE: Minimal hepatic encephalopathy; PQSI: Pittsburgh Sleep Quality Index

On the day of PHES and EncephalApp tests, some of the patients presented with common complications of cirrhosis such as ascites, portal thrombosis, anaemia and thrombocytopenia [Table 1]. Laboratory values of ammonia, haemoglobin, serum sodium, C-reactive protein and creatinine are also presented in Table 1.
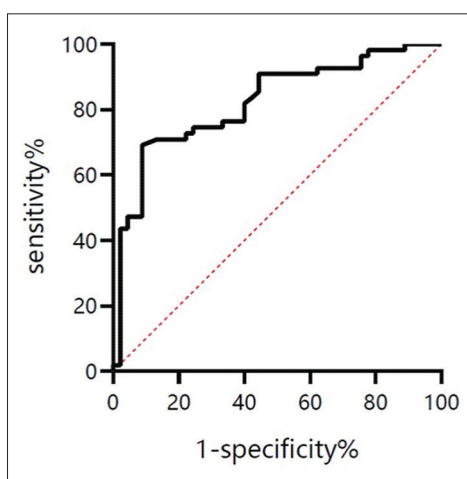
Figure 2: Receiver–operator curves (ROC) for EncephalApp in the diagnosis of minimal hepatic encephalopathy. The area under the ROC of EncephalApp was above 0.7, indicating that EncephalApp could distinguish cirrhotic patients with and without MHE very well

Diagnostic efficiency of the EncephalApp

Using the PHES as the reference standard, 98 patients (54.4%) were diagnosed with MHE. The remaining 82 patients were not considered to have MHE. The total Off-time, total On-time and total Off-time plus On-time of EncephalApp in cirrhotic patients with MHE were significantly higher than those without MHE ($P < 0.05$). However, there was no significant difference in median trials for five 'off' correct runs and five 'on' correct runs between cirrhotic patients with and without MHE ($P > 0.05$) [Table 2]. Meanwhile, ROC analysis showed that the threshold value for the total Off-time plus On-time of EncephalApp was 225.60 s, and EncephalApp had a sensitivity of 85.2% and specificity of 77.3%, with AUC of 0.864 [Figure 2].

Predictors of poor sleep quality in MHE

PSQI scores of cirrhotic patients with MHE were significantly higher than those without MHE ($P < 0.05$). Compared with cirrhotic patients without MHE, the scores of sleep quality, sleep latency, sleep duration and sleep disturbances were significantly higher in those with MHE ($P < 0.05$). However, there was no statistical difference in daytime dysfunction and habitual sleep efficiency [Table 2].

Table 3: Univariate and multivariate analyses of independent predictors of PSQI score in MHE patients

	PQSI scores		Univariate analysis		Multivariate analysis		
	>5	≤5	t/χ^2	P	β	P	OR (95% CI)
Number of patients	62	36					
Age (years)	56 (28-65)	55 (29-69)	0.88	0.38			
Gender (male/female)	32/30	21/15	0.41	0.52			
Education (years)	9 (5-16)	9 (5-15)	-0.57	0.53			
Body mass index (BMI)	21.0 (16.5-31.8)	21.9 (17.2-32.2)	0.56	0.34			
Child-Turcotte-Pugh grade (A/B/C)	48/12/2	29/6/1	6.98	0.03	1.74	<0.01	2.11 (1.55, 2.85)
MELD scores	11.7±3.82	8.22±3.67	3.20	<0.01	1.35	0.33	1.83 (0.94, 3.35)
Ammonia (µmol/L)	60.6±8.50	48.6±6.35	6.06	<0.01	-0.32	0.54	0.93 (0.55, 2.16)
HBV-DNA (positive/negative)	32/30	20/16	0.45	0.19			
Haemoglobin (g/L)	126±25	123±31	0.52	0.60			
Serum sodium (mmol/L)	137±8.75	138±7.92	-0.57	0.57			
C-reactive protein (mg/L)	7.61±2.35	4.83±2.12	5.98	<0.01	1.09	0.25	1.12 (0.89, 1.35)
Creatinine (µmol/L)	60.5±18.4	56.0±20.5	1.12	0.27			
PHES results	-8.54±2.25	-6.86±2.15	2.68	0.01	0.89	0.18	1.57 (0.85, 2.76)
Total On-time plus Off-time (s)	260.8±50.4	232.9±48.5	2.68	0.01	2.76	<0.01	4.14 (1.95, 6.29)

MHE: Minimal hepatic encephalopathy; PQSI: Pittsburgh Sleep Quality Index

Using the PSQI scores >5 as the threshold value to distinguish good and poor sleep quality, 62 cirrhotic patients (63%) with MHE were diagnosed as poor sleepers, and the remaining 36 patients were considered good sleepers. The univariate analyses of demographic variables, clinical profile, PHES results, EncephalApp results and sleep quality between MHE patients with poor sleep quality and those with good sleep quality are shown in Table 3. Significant differences were found concerning MELD scores, CTP grades, PHES results, the total Off-time plus On-time of EncephalApp, plasma levels of ammonia and serum levels of C-reactive protein between cirrhotic patients with and without MHE ($P < 0.05$). By contrast, age, sex, education levels, BMI, haemoglobin, serum sodium levels, creatinine and HBV-DNA levels did not differ significantly ($P > 0.05$). The backward conditional stepwise logistic regression analysis showed the CTP grades (Odds ratio [OR] = 2.11 (1.55–2.85), $P < 0.01$) and the total Off-time plus On-time of EncephalApp (OR = 4.14 (1.95–6.29), $P < 0.01$) were independent predictors of poor sleep quality in patients with MHE.

Among patients with MHE having poor sleep quality, the total Off-time plus On-time of EncephalApp

Table 4: Correlation between PQSI scores and total Off-time plus On-time in MHE patients with poor sleep quality

PQSI scores	Total Off-time plus On-time (s)	
	r	P
Sleep quality	0.26	0.02
Sleep latency	0.35	0.08
Sleep duration	0.67	0.03
Habitual sleep efficiency	0.58	0.46
Sleep disturbances	0.43	<0.01
Use of sleep medication	0.51	0.18
Daytime dysfunction	0.24	0.02

MHE: Minimal hepatic encephalopathy; PQSI: Pittsburgh Sleep Quality Index

were associated with sleep quality, sleep duration, sleep disturbances and daytime dysfunction. However, the total Off-time plus On-time of EncephalApp were not associated with sleep latency, habitual sleep efficiency and use of sleep medication [Table 4].

DISCUSSION

We found that the total Off-time plus On-time of EncephalApp correlated with sleep quality. The total Off-time plus On-time of EncephalApp is an independent predictor of poor sleep quality in patients with MHE due to hepatitis B-induced cirrhosis. EncephaApp is a point-of-care alternative for the diagnosis of MHE and the administration of the test requires only 15 min. Compared to the PSQI, the use of EncephalApp may conveniently and rapidly identify MHE and predict poor sleep quality in patients with MHE, which is very important for early prevention and subsequent treatment of MHE.

EncephalApp has been found to have good diagnostic validity for MHE in patients with cirrhosis. When using PHES as the reference standard in the American population, EncephalApp had a sensitivity of 80% and specificity of 90% for diagnosing MHE and thus, identified MHE with an AUROC value of 0.8 in cirrhotic patients without prior overt HE.[13,14] Similarly, the present study showed that EncephalApp attained 85.2% sensitivity and 77.3% specificity, with AUC greater than 0.8, suggesting that EncephalApp has a high diagnostic value for MHE in the Chinese cirrhotic population with hepatitis B virus infection. PHES and EncephalApp were found to be equivalent for diagnosing MHE, suggesting that single testing with EncephalApp is sufficient for diagnosing MHE in clinical practice.[23]

The major aetiology of cirrhosis in China is hepatitis B, and that of the United States is chronic alcohol abuse. Although the aetiologies of cirrhosis in China are different from those of the United States, EncephalApp showed similar sensitivity, specificity and AUC, suggesting that the availability of EncephalApp may not be influenced by the different aetiologies of cirrhosis. We also found that EncephalApp results were not affected by age, sex or educational background in Chinese cirrhotic patients. However, age and educational background were reported to be significant influencing factors for EncephalApp results in multicentre studies with American cirrhotic patients.[12-14] This discrepancy suggests that the generalisability of EncephalApp requires further validation with larger Chinese populations in multicentre studies.

Cirrhotic patients with MHE have sleep abnormalities such as poor sleep quality, increased day time sleepiness and more nocturnal sleep arousals, compared to patients without MHE.[15] Previous studies have found that results of diagnostic methods of MHE correlate with the sleep quality in patients with MHE. For example, Samanta *et al.* found a correlation between PHES results and PSQI scores in such patients.[16] Xiao *et al.* showed a correlation between NCT-A results and PSQI scores in patients with cirrhosis induced by hepatitis B.[24] Similarly, we found that cirrhotic patients with MHE had worse EncephalApp results, considered as one of the independent predictors for poor sleep quality in these patients. The correlation may be attributed to poor sleep quality of MHE being associated with the specific neuropsychiatric impairments that can be exactly evaluated by EncephalApp.[16]

We found that the total Off-time and On-time of EncephalApp are associated with sleep quality, sleep duration, sleep disturbances and daytime dysfunction in patients with MHE. Functional magnetic resonance imaging (MRI) showed that the performance of the Stroop test indirectly reflects the activation and inhibition of cerebral neural nuclei in the bilateral anterior cingulate, left inferior frontal regions and bilateral parietal regions.[25,26] The activation and inhibition of these related neural nuclei play important roles in the regulation of sleep mechanism in rapid eye movement (REM) sleep phase.[27] Patients with poor sleep quality have decreased REM sleep phase compared with cirrhotic patients without MHE and those with good sleep quality.[28] In the presence of MHE, an inhibitory neurotransmitter called gamma-aminobutyric acid, and cerebral levels of ammonia are increased. Gamma-aminobutyric acid inhibits the activation of cerebral nerve nuclei in the bilateral anterior cingulate and left inferior frontal regions of the brain.[29] Moreover,

hyperammonaemia increases the intracellular content of glutamine, resulting in astrocyte swelling which leads to low-grade cerebral oedema that might impair the regulation of the activation and inhibition of neural nuclei in the left inferior frontal regions and bilateral parietal regions of the brain.[30,31] Furthermore, hyperammonaemia activates microglia and induces further neuroinflammation that interferes with the inhibition of related nerve nuclei, subsequently disturbing the rhythm of sleeping and waking in REM sleep phase, which is closely associated with sleep duration and changes in the daytime function of PSQI scores.[32]

There are limitations to this study. Firstly, included patients were enrolled from a single centre of hepatology, which may induce referral bias. Future multicentre studies including the validation group would evaluate the validity and generalisation of the conclusion. Moreover, we only included patients with MHE due to hepatitis B-induced cirrhosis. Patients with alcoholic cirrhosis showed more serious cognitive impairment in the EncephalApp results, despite similar severity of cirrhosis.[12] Thus, the conclusion may not be generalisable to patients with alcoholic cirrhotic patients without abstinence. Furthermore, the sleep quality of these patients was only evaluated on one defined day, and not every clinical symptom of MHE may be present at a given time. Thus, future longitudinal investigations with repeated evaluations are necessary for the fluctuation of sleep quality in patients with MHE.

In conclusion, EncephalApp is a convenient, simple and highly sensitive test for diagnosing MHE which can predict poor sleep quality in patients with MHE due to hepatitis B-induced cirrhosis. Application of EncephalApp may help in the early identification of MHE with poor sleep quality in high-risk cirrhotic patients. Furthermore, treatment of MHE with lactulose or probiotics not only relieves mental symptoms but also improves sleep quality in cirrhotic patients.[33,34] Thus, the early utility of these therapeutic options in MHE patients with poor sleep quality identified by EncephalApp may lead to improvement of sleep quality. Therefore, sleep quality is an important part of health-related QoL. Besides, whether EncephalApp results can evaluate the full spectrum of health-related QoL of patients with MHE requires to be investigated in future studies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will

not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

There are no conflicts of interest.

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