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ORIGINAL ARTICLE

Role of Excessive Daytime Sleepiness in Diagnosis of Minimal Hepatic Encephalopathy in Patients with Liver Cirrhosis

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ABSTRACT

Background: Minimal hepatic encephalopathy (MHE) is a serious complication in cirrhotic patients necessitating many precautions. Sleep disturbances like excessive daytime sleepiness (EDS) are common among cirrhotic patients and have deleterious effects on their quality of life. There are many questionnaires designed to diagnose sleep disturbances like Epworth Sleepiness Scale (ESS) which is designed to assess daytime sleepiness. The aim of this study is to assess the role of EDS measured by ESS in the diagnosis of MHE in patients with liver cirrhosis.

Methods: A total of eighty cirrhotic patients were included in this study. They were divided according to psychometric hepatic encephalopathy score (PHES) results into two groups group I: forty patients with MHE and group II: forty patients without MHE. The ESS model was applied to the patients of both groups and their results were compared.

Results: The results of ESS and the frequency of patients suffering from EDS were higher in group I compared to group II but without statistically significant difference. Using the AUROC test ESS, at a cut-off value of 6, could predict the presence of MHE with 80% sensitivity and 45% specificity.

Conclusions: There is no significant association between EDS, measured by ESS, and the presence of MHE in cirrhotic patients without overt hepatic encephalopathy (OHE). ESS is not accurate in predicting the presence of MHE.

Keywords: Minimal hepatic encephalopathy; psychometric hepatic encephalopathy score; excessive daytime sleepiness; Epworth Sleepiness Scale

INTRODUCTION

MHE is a serious condition having multiple deleterious effects on patients' daily activities and quality of life including driving impairment and traffic accidents. It has also negative impacts on work performance especially in patients having complex occupational tasks [1]. It is important to diagnose MHE as early as possible and to start treatment immediately to minimize its dangerous consequences on patients and the community [2]. MHE diagnosis is difficult as it is not clinically evident and needs special tests to be identified [3]. PHES is the gold standard tool for the diagnosis of MHE but needs educated patients to be performed [4]. Sleep disturbances are common among cirrhotic patients and have significant effects on their

quality of life. Common complaints regard to sleep is prolonged time to fall asleep, shortened sleep duration, daytime sleepiness, poor sleep quality, and frequent nocturnal awakenings [5]. Reversal of sleep rhythm is recognized as one of the early signs of hepatic encephalopathy (HE) [6]. The pathophysiological mechanisms of these disturbances are not fully understood. Earlier studies showed that patients with liver cirrhosis have higher melatonin levels throughout the day and delayed onset of melatonin peaking during the night [7]. There are limited studies assessing the relationship between sleep disturbances and the level of neuropsychiatric impairment in cirrhotic patients without OHE.

There are many questionnaires designed to assess sleep quality. ESS is used to assess daytime sleepiness [8].

We aimed in this work to assess the role of EDS measured by ESS in the diagnosis of MHE in patients with liver cirrhosis.

METHODS

Patients and Methods:

This case-control study was conducted in Tropical Medicine Department, Zagazig University Hospitals during the period from November 2017 to July 2018. This study included 80 cirrhotic patients without OHE, who were admitted to Tropical Medicine Department, at Zagazig University Hospitals, during this period. They were classified, according to the results of PHES into two groups: Group I: comprised 40 cirrhotic patients with MHE. They were 28 males and 12 females. Their age ranged from 43 to 60 years. Group II: comprised 40 cirrhotic patients without MHE. They were 23 males and 17 females. Their age ranged from 23 to 60 years. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria:

Patients diagnosed with liver cirrhosis based on the combination of clinical, radiological, and laboratory data were included in the study.

Exclusion criteria:

Patients who were less than 18 years old and more than 60 years old to avoid age related sleep disorders [9] and affection of PHES [10], illiterate patients who are unable to perform the psychometric tests, history or the presence of OHE, history of other neuropsychiatric disorders e.g. cerebrovascular stroke, history of other severe medical problems e.g. renal impairment, congestive heart failure or pulmonary disease, history or presence of endocrinal diseases causing sleep disturbances like thyrotoxicosis and hypothyroidism [11], presence of metabolic diseases causing sleep disturbances like DM and obesity [12], presence of hepatocellular carcinoma (HCC), history of recent (< 6 weeks) gastrointestinal bleeding, presence of symptoms and signs suspecting obstructive sleep apnea (OSA), history of alcohol intake or abstinence from alcohol for less than 3 months, history of recent (< 6 weeks) intake of drugs affecting the psychometric performance like benzodiazepines, anti-epileptic and other psychotropic drugs, history of shunt surgery, patients whose jobs include night shifts and patients who did not give informed consent to participate in the study

Study measurements:

Full history taking: with stress on age, history of medical diseases or surgeries, history of drug intake, history of attacks of hematemesis or melena, and history of previous hepatic encephalopathy.

Thorough clinical examination including general examination and local abdominal examination with a focus on signs of chronic liver disease. In addition to ENT examination which was done to rule out the presence of symptoms and signs of OSA.

Neurological examination including mental status assessment with special attention to alteration of consciousness, memory, cognition, and concentration.

Psychiatric evaluation: to exclude patients with major psychiatric disorders like psychosis and anxiety disorders.

Laboratory investigations including CBC (hemoglobin level, RBCs count, WBCs count,

and platelet count), liver function tests (total and direct bilirubin, total protein, serum albumin, AST and ALT), kidney function tests (BUN and serum creatinine level), Coagulation profile (prothrombin time and INR) and serum sodium and potassium levels.

Pelviabdominal ultrasonography: for diagnosis of cirrhosis and portal hypertension, detection of ascites, detection of the presence of portosystemic collaterals, and screening for HCC.

Child-Turcotte -Pugh classification: to assess the severity of liver disease [13].

Psychometric hepatic encephalopathy score (PHES) [4]: to diagnose patients with MHE. The two tests used in this study were: the number connection test A (NCT A) and the digit symbol test (DST). We applied the tests to two of the patients' apparently healthy relatives who had close age, environment, and educational levels. Their results were used as a reference for assessing the patients' results as PHES is still not standardized for the Egyptian population. Number connection test A (NCTA): It measures cognitive-motor abilities. Subjects were instructed to connect numbers serially from 1 to 25 (written in Arabic, printed haphazardly on paper) with identification of both the starting and finishing points as quickly as possible. The test score was the time in seconds required to complete it, including the time needed to correct any error. It was considered abnormal when the time taken by patients was greater than the mean plus 2SD of that recorded by the healthy controls. Digit symbol test (DST): Subjects were given a series of double boxes with a number given in the upper part. The task was to draw a symbol pertinent to this number into the lower part of the boxes. Nine fixed pairs of numbers and symbols were given at the top of the test sheet. The test score was the total number of correct sequential matching of symbols to numbers in a 90-second interval. The test was in Arabic. It was considered abnormal when the score gained by the patients was less than the mean minus 2SD from that of the healthy controls.

Sleep-wake profile:

Epworth Sleepiness Scale (ESS): This scale is used to assess daytime sleepiness by asking patients about the chance of "dosing off" in eight different daytime situations including sitting and reading, watching TV, sitting inactive in public places, lying down rest in the afternoon, as a passenger in a car for an hour without a break, sitting and talking to someone, in a car while stopped for a few minutes in traffic and sitting quietly after lunch without alcohol on a scale from 0 to 3:

0→ would never fall asleep in that situation

1→ there is a slight chance of falling a sleep

2→ there is a medium chance

3→ there is a high chance

Then, the scores were summated to form a total score ranging from 0 to 24. A score of ≥ 11 is considered abnormal and has EDS [8].

Statistical analysis

The data were analyzed using the SPSS epi info 8 versions. The qualitative data were represented as numbers and percentages and were compared using the chi-square test. The quantitative data were represented as mean and standard deviation and compared using the t-test for normally distributed data and Mann-Whitney when data wasn't normally distributed. ANOVA was used for the analysis of more than two variables. The study of the clinical performance was done using the area under the ROC curve.

RESULTS

Table 1 shows that there were no significant differences between the studied groups as regards the demographic data and the cause of cirrhosis. Table 2 shows that the presence of portosystemic collaterals was significantly more frequent in group I patients when compared to group II patients. There were no significant differences between the two groups as regards clinical data, the remaining sonographic findings, and Child's score and grade. Table 3 shows that potassium level was significantly lower among group I patients when compared to group II patients. There were no significant differences between the two groups as regards the remaining laboratory parameters. Table 4 shows the comparison

between the studied groups as regards their ESS score and the frequency of patients having EDS among them. It revealed that the ESS score was higher in group I patients than in group ΠI patients but without a statistically significant difference. It also revealed that group I had a higher frequency of patients having EDS than group ΠI but without a statistically significant difference. Table 5 shows that there was no significant correlation between the ESS score and the Child's score in the studied groups. Table 6 and Figure 1 represent the clinical performance of ESS score as a predictor of MHE. It shows that at the cut-off value > 6 ESS, in the absence of other causes of sleep disturbances, could predict the presence of MHE with 80% sensitivity and 45% specificity.

Table 1: Demographic data and cause of cirrhosis among the studied groups.

		Group I N=40	Group II N=40	X^2	P
Age, years	**Mean±SD**	51.8 ± 5.7	52.4 ± 7.5	-1.3 *	0.209(NS)
Sex	**F**	12 (30%)	17 (42.5%)	1.4	0.245(NS)
	M	28 (70%)	23 (57.5%)		
Cause of cirrhosis	**HCV**	38 (95%)	38 (95%)	4.0	0.261(NS)
	HBV	2 (5.0%)	0 (0%)		
	HBV,HCV	0 (0%)	1 (2.5%)		
	AIH	0 (0%)	1 (2.5%)		

Table 2: Clinical data, sonographic findings, and Child's score and grade among the studied groups.

		Group I N=40	Group II N=40	X^2	P
Jaundice	**Absent**	23 (57.5%)	27 (67.5%)	0.8	0.355(NS)
	Present	17 (42.5%)	13 (32.5%)		
LL edema	**Absent**	10 (25%)	13 (32.5%)	0.5	0.458(NS)
	Present	30 (75%)	27 (67.5%)		
Liver	**Average size**	6 (15%)	9 (22.5%)	1.5	0.463 (NS)
	Enlarged	3 (7.5%)	5 (12.5%)		
	Shrunken	31 (77.5%)	26 (65%)		
Spleen	**Removed**	1 (2.5%)	0 (0%)	0.5	0.974(NS)
	Average	22 (55%)	24 (60%)		
	Enlarged	17 (42.5%)	16 (40%)		
Grade of ascites	**No**	11 (27.5%)	13 (32.5%)	8.2	0.082(NS)
	Minimal	2 (5%)	1 (2.5%)		
	Mild	2 (5%)	9 (22.5%)		
	Mod	21 (52.5%)	14 (35%)		
	Tense	4 (10%)	3 (7.5%)		
Collaterals	**Absent**	22 (55%)	33 (82.5%)	7.0	**0.015(S)**
	Present	18 (45%)	7 (17.5%)		
Child grade	**A**	6 (15%)	11 (27.5%)	4.4	0.113(NS)
	B	12 (30%)	16 (40%)		
	C	22 (55%)	13 (32.5%)		
Child Score	**Mean±SD**	8.7 ± 2	8 ± 2.1	-1.8 *	0.079(NS)

Table 3: Laboratory parameters of the studied groups.

	Group I N=40	Group II N=40	T	P
Hb, g/dl	10.2 ± 2.1	9.6 ± 1.8	-1.5	0.144(NS)
WBC, x10³/L	7.3 ± 4.6	6.5 ± 3	-3.1	0.067(NS)
PLT, x10³/L	110.8 ± 76.5	103.6 ± 69.1	-0.3	0.744(NS)
T.Bil mg/dL	3.6 ± 1.9	2.9 ± 2.0	-2.1	0.092(NS)
D.Bil mg/dL	3.1 ± 5	1.6 ± 2.2	-1.9	0.058(NS)
T.Protien g/dL	6.6 ± 0.9	6.4 ± 0.8	-1.0	0.305(NS)
S.Albumin g/dL	2.7 ± 0.6	2.9 ± 0.6	-1.7	0.083(NS)
AST, IU/L	71.2± 62.4	65 ± 79.6	-1.5*	0.127(NS)
ALT, IU/L	37 ± 21.3	36.2± 41.2	-1.6*	0.118(NS)
INR	1.6 ± 0.3	1.4 ± 0.3	-0.6	0.564(NS)
S.Cr., mg/dL	0.9 ± 0.4	0.8 ± 0.3	-1.4*	0.168(NS)
BUN, mg/dl	23.56±6.07	19.7±4.6	-0.9	0.435(NS)
Na, mEq/L	135± 9	136.1± 11.2	-0.01	0.992(NS)
K, mEq/L	3.2 ± 0.7	4.1 ± 0.7	-2.1	**0.033(S)**

Table 4: ESS of the studied groups.

		Group I N=40	Group II N=40	Test	P
ESS	**EDS**	13 (32.5%)	8 (20%)	5.2	0.16(NS)
	No EDS	27 (67.5%)	32 (80%)		
ESS score	**Mean±SD**	9.4 ± 4.1	8.3 ± 4.4	-1.7*	0.097(NS)
	Median(range)	9 (2-19)	7 (2-20)		

Table 5: Correlations between ESS score and CTP score in the studied groups.

	Group I N=40		Group II N=40	
	ESS score		ESS score	
	R	P	r	P
CTP Score	0.155	0.339(NS)	-0.115	0.482(NS)

Table 6: Clinical performance of ESS as a diagnostic test for MHE

	ESS score
Cut_off	>6
Sensitivity 95% Confidence interval (CI)	80 64.4 - 90.9
Specificity 95% CI	45 29.3 - 61.5
Positive predictive value (PPV) 95% CI	59.3 45.0 - 72.4
Negative predictive value (NPV) 95% CI	69.2 48.2 - 85.7
Area under the ROC curve (AUC)	0.607
P	0.0946

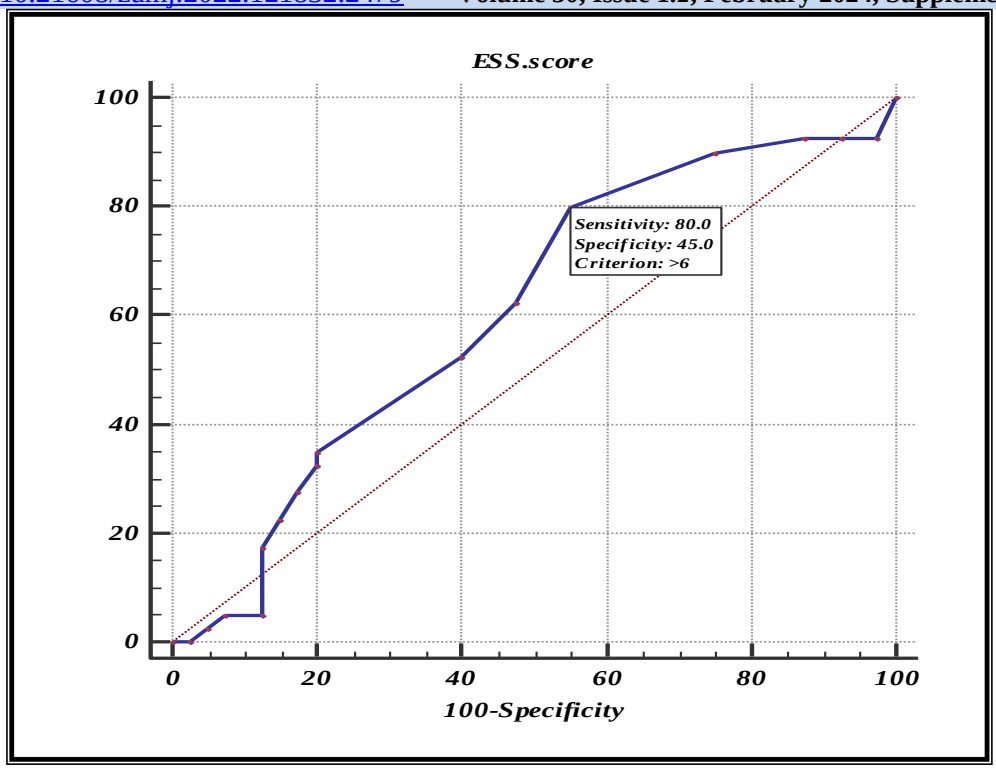

Figure 1: ROC curve representing the clinical performance of ESS score as a predictor of MHE.

DISCUSSION

This study revealed that the presence of portosystemic collaterals, revealed by ultrasonographic examination, was more frequent among group I patients when compared to group II patients with a statistically significant difference. This comes in agreement with the results of Riggio et al., [14]. The increased frequency of collaterals seems to play a role in the pathogenesis of MHE in those patients [15]. This study showed that patients with MHE had significantly lower potassium levels when compared to that of the second group. This comes in agreement with the results of Kumar et al., [16]. This is a demonstration of the role of hypokalemia as a precipitating factor of HE [17]. In contrary to this, Samanta et al., [18] did not find any significant difference between the two groups. This could be explained by the inequality of the number of patients in each group in his study which comprised fewer patients with MHE so the difference between the two groups was not clear. When the two groups were compared as regards their ESS score and the frequency of patients with EDS among them, it was found that the ESS score was higher in group I patients than in group II patients, but without significant difference. It was also found that the MHE group had a higher frequency of patients having EDS than group II but without a statistically significant difference. This comes in agreement with Montagnese et al., [19] who did not find a significant relation between EDS and the presence of HE. This is contrary to the results of Samanta et al., [18] and Singh et al., [20] who found that there was a significant correlation between EDS and MHE. This finding can be explained by excluding patients who had signs of HE or those with a history of previous episodes of HE from the study and it is previously known that inverted sleep rhythm is one of the early signs of HE [6]. This explanation could be supported by other studies that revealed that EDS was associated with a history of HE and an increased risk of HE-related hospitalization [21, 22]. There was no significant correlation between the ESS score and the CTP score among the studied groups. This comes in agreement with the results of Mostacci et al., [6]. Montagnese et al., [17] also did not find any significant correlation between the ESS score and the Child's grade of the studied population. But Samanta et al., [18] found that there was a significant correlation between the ESS score and the Child grade of the studied population. The explanation for this finding could be that the ESS score is poorly linked to the severity of liver disease. This study revealed that the ESS score, at

a cut-off value of > 6, could predict the presence of MHE with 80% sensitivity and 45% specificity. To our knowledge, no previous study has calculated the cut-off value at which the ESS score could predict the presence of MHE in Egyptian patients.

CONCLUSION

From the present study, it can be concluded that there is no significant association between sleep disturbances in the form of EDS and the presence of MHE in cirrhotic patients without OHE. It is also concluded that ESS is not very accurate in predicting the presence of MHE. It is recommended to perform further studies by using other sleep evaluating tests to accurately assess the relationship between sleep disturbances and MHE in cirrhotic patients without OHE.

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