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ORIGINAL ARTICLE

Frequency and Risk Factors of Minimal Hepatic Encephalopathy Among Patients with Compensated Cirrhosis.

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ABSTRACT

Background: Minimal hepatic encephalopathy (MHE) has a mild neurocognitive impairment that includes neuropsychological and neurophysiological alterations that can not be detected by clinical examination. This study aims to assess the frequency and risk factors for developing minimal hepatic encephalopathy in patients with compensated cirrhosis. **Methods:** This cross sectional study was conducted on 60 patients with compensated cirrhosis in Zagazig University Hospital and elmatarya Teaching Hospital from December 2017 to June 2018, diagnosis of minimal hepatic encephalopathy was established by using mini mental status examination test and psychometric studies, they underwent full history, laboratory investigations and abdominal doppler ultrasonography by professional radiologist assessing the presence of any porto systemic shunts and measuring serum ammonia level. **Results**: About 37% had MHE. Female represented 65% with mean age 49.82 years. There is statistically significant relation between MHE and smoking, comorbid diabetes, hypertension, high ammonia level and portosystemic shunt. Smoking, being single, illiterate, portosystemic shunt, comorbid diabetes and hypertension increased risk of MHE by 4.57, 3.05, 2.31, 25.94, 3.29 and 3.55 folds. Male gender and normal ammonia level were protective factors. There is significant relation between MHE and age, platelet count, serum albumin, ammonia and INR. Older patients, low platelet count and serum albumin, high ammonia level and INR were detected among patients with MHE. Increasing ammonia level was significant independent risk factor for MHE. **Conclusions:** MHE is a prevalent condition among patients with compensated cirrhosis with high ammonia level and portosystemic shunts as a strong risk factors for its development.

Keywords: hepatic encephalopathy; shunt; ammonia

INTRODUCTION

Minimal hepatic encephalopathy has a moderate neurocognitive disorder that involves neuropsychological and neurophysiological changes that can not be identified through clinical review [1]. MHE is the mildest type inside the spectrum of hepatic encephalopathy (HE). MHE is viewed as the initial phase of the hepatic encephalopathy process. This causes up to 80 per cent of cirrhosis patients [2].

MHE can be observed in patients with

cirrhosis and in non-cirrhosis patients with Porto systemic shunting that affecting up to 80% of patients with cirrhosis [3]. MHE has a negative impact on day-to-day activities and workability affects health-related quality of life [4] impairs driving fitness[5], associated with motor vehicle crashes[6] and predisposes the patient to fall[7]. In addition, MHE is of prognostic significance as it is a risk factor for overt HE development [8] and death.

Recognizing MHE and its risk factors is important because its treatment can improve cognitive functions [9] and quality of life [10] and avert progression to overt HE [11].

The initial indications for studying whether a patient is at risk of MHE are problems of quality of life and complaints from relatives and caregivers. Ideally, patients at imminent risk should be evaluated, including those with previous episodes of HE, cirrhotic patients and those performing risky public activities such as bus drivers [12-13]. There is actually no gold standard for MHE diagnosis, because it impacts multiple cognitive functioning pathways that do not generally deteriorate similarly. The ISHEN (International Society for Hepatic Encephalopathy and Nitrogen metabolism) advises at least two different tests for diagnosis [14]. MHE identification methods are classified into two main types: psychometric and neuropsychological studies [15].

The aim of this work is to identify the frequency and risk factors associated with development of minimal hepatic encephalopathy among patients with compensated cirrhosis.

METHODS

The work has been carried in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsiniki) for studies involving humans. A written informed consent was handled from the patient to contribute in the study. Approval for carrying out the work was received from the Departments of Internal Medicine and Clinical Biochemistry, University Hospitals of Zagazig, after obtaining an academic review board.

Study Design, Study Setting, and Study Participants

This is a cross sectional study conducted in elzagazig University Hospital and elmataria teaching hospital from December 2017 to June 2018.

Patients included in the study: Comprehensive sample of sixty patients with compensated cirrhosis who fulfilled the inclusion criteria .

Inclusion criteria: Adult patients of both genders (aged 18 to 60 years old). Serum albumin ≥3.5gm/dl, serum INR≤ 1.7, Serum bilirubin ≤ 2gm/dl, Absence of ascites or HCC.

Exclusion criteria: Decompensated cirrhosis. Patients who refuse to participate in the study

Study tools and data collection: Complete history taking and Clinical examination were performed for all patients.

Laboratory investigations were done to verify eligibility of patients to be included in the study and identify potential risk factors: Routine investigations:, Complete blood picture, erythrocyte sedimentation rate, random blood glucose. Viral markers : HBS Ag, HCV- Ab

Complete liver biochemical profile: Serum bilirubin (total and direct), Liver enzymes (AST and ALT), Serum albumin, total proteins, Prothrombin time, concentration and INR. Kidney function (Urea and Creatinine).

Blood ammonia level:

Radiological investigation: Abdominal doppler ultrasound to assess: portal vein diameter, presence of any porto systemic shunts (collaterals), liver parenchyma, ascites, splenomegaly and any other significant sonographic data.

Mini-mental state examination to identify MHE (occult neurosychiatric and cognitive abnormalities) [16]: A brief 30- point questionnaire used for quantitative measurement. of cognitive status in adults. The total score of the test is 30. Any score over 27 is considered normal. Scores between (20-26) indicate some cognitive impairment. Scores between (10-19) indicates moderate to severe cognitive impairment. Scores below 10 indicate severe cognitive impairment .

Number connection test A(NCT A)[17]: In this test, numbers are arranged in a random

series and must be related to each other in their correct sequence as quickly as possible, using pencil to draw line between them. The test is designed to help healthy people to perform this task in under 45 seconds (taking in consideration his age and education level). If the patient takes more than the given time, MHE can be diagnosed with high sensitivity.

Case definition of MHE: Neuropsychological and neurophysiological abnormalities that are not detectable from the clinical evaluation usually used to identify the presence of MHE; these include cognitive and attention deficits, loss of inhibitory response, loss of working memory and lack of visuomotor coordination. Patients with MMSE score less than 27 and more than 2 seconds above the limited time in NCT (talking in consideration age and education level) are included.

Statistical Analysis:

All data for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium) were gathered, tabulated and statistically analyzed using SPSS 20.0. Using the Shapiro Walk test the data was tested for normal distribution. Qualitative data as frequencies and relative percentages were symbolized. Used for the measurement of disparity between qualitative variables, the Chi square method (Š2). Quantitative results as mean ± SD (standard deviation) have been published. Mann Whitney test was used to compare two-group medians (for nonparametric data).Independent sample t test was used to compare two-group information. The study of conditional logistic regression has been used to classify risk factors for the growth of MHE. Level of P-value ≤ 0.05 is significant and p ≤0.001 is highly significant difference.

RESULTS

About 37% of the studied patients had MHE (Table 1). Half of them were diabetic and the same percentage were smokers. Forty percent of them had comorbid hypertension. About 58% and 77% of them were educated and married. Ninety five percent had hepatitis C. Portosystemic shunt and high ammonia level were present in 63.3% and 88.3%. There is statistically significant relation between presence of MHE and all of smoking, comorbid diabetes, hypertension, high ammonia level and portosystemic shunt. There is statistically non-significant relation between MHE and either education, type of hepatitis, being single, illiterate. Male gender and normal ammonia level were protective factors (Table 2)

Mean age of the studied patients was 49.82 years. There is significant relation between MHE and all of age, platelet count, serum albumin, ammonia and INR. Older patients, low platelet count, low serum albumin, high ammonia level and elevated INR were detected among patients with MHE. On the other hand, there is non-significant relation between MHE and either hemoglobin level, TLC, ALT, AT or total bilirubin (table 3).

Increased ammonia level was a significant independent risk factor for MHE in patients with compensated cirrhosis where it increased the risk by 4.06 folds (table 4)

Table 1. Distribution of the studied patients according to presence of MHE

MHE	N=60	%
Absent	38	63.3
Present	22	36.7

Table 2. Relation between presence of MHE and the studied parameters

	Total	MHE		p	OR (95% CI)
	N=60	Yes (n=22)	No (n=38)		
Gender:					
Male	21 (35)	4 (19)	17 (81)	0.051	0.28(0.08-0.97)
Female	39 (65)	18 (46.2)	21 (53.8)		
Smoking:					
No	30 (50)	6 (20)	24 (80)	0.007*	4.57(1.45-14.39)
Yes	30 (50)	16 (53.3)	14 (46.7)		
Education:					
Illiterate	25 (41.7)	12 (48)	13 (52)	0.124	2.31 (0.79 – 6.76)
Educated	35 (58.3)	10 (28.6)	25 (71.4)		
Marital status:					
Single	14 (23.3)	8 (57.1)	6 (42.9)	0.069	3.05(0.89 -10.35)
Married	46 (76.7)	14 (30.4)	34 (69.6)		
Diabetes:					
Absent	30 (50)	7 (23.3)	23 (94.6)	0.032*	3.29(1.08 - 9.95)
Present	30 (50)	15 (50)	15 (50)		
Hypertension:					
Absent	36 (60)	9 (25)	27 (75)	0.03*	3.55(1.18-10.67)
Present	24 (40)	13 (54.2)	11 (45.8)		
Hepatitis:					
HbSAg positive	3 (5)	1 (33.3)	2 (66.7)	>0.999	1.17(0.1- 13.66)
HCV RNA positive	57 (95)	21 (36.8)	36 (63.2)		
Portosystemic shunt:					
Absent	22 (36.7)	1 (4.5)	21 (95.5)	<0.001**	25.94(3.16 - 213.02)
Present	38 (63.3)	21 (55.3)	17 (44.7)		
Ammonia level:					
Normal	7 (11.7)	0 (0)	7 (100)	<0.001**	0
High	53 (88.3)	22 (41.5)	31 (58.5)		

Table 3. Relation between presence of MHE and both age and laboratory data of the studied patients

Parameters	Total	MHE		Test	
		Present	Absent	t	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)	49.82±8.39	53.55±5.12	47.66 ± 9.19	2.761	0.008*
Hemoglobin (g/dL)	12.38 ± 1.73	12.18 ± 1.37	12.5 ± 1.91	-0.684	0.497
TLC (103/mm3)	6.8 ± 1.66	6.33 ± 1.85	7.08 ± 1.5	-1.718	0.091
Platelet count (103/mm3)	205.75 ±44.77	182.36±32.99	219.29±45.44	-3.332	0.002*
ALT (U/L)	42.34 ± 18.74	38.41 ± 20.43	44.62 ± 17.57	-1.242	0.219
AST (U/L)	44.29 ± 18.52	39.41 ± 18.24	47.12 ± 18.34	-1.572	0.121
Total bilirubin (mg/dL)	0.78 ± 0.21	0.76 ± 0.23	0.8 ± 0.2	-0.719	0.475
Serum albumin (g/dL)	3.82 ± 0.25	3.7 ± 0.24	3.89 ± 0.23	-3.067	0.003*
Ammonia (mg/dL)	63.52 ±10.27	73.64 ± 4.89	57.66 ± 7.64	4.193	<0.001**
INR	1.12 ± 0.18	1.24 ± 0.21	1.04 ± 0.09	8.801	<0.001**

*p<0.05 is statistically significant

Table 4. Logistic regression of factors associated with MHE among the studied patients

	β	p	Odds Ratio	95% Confidence interval	
				Lower	Upper
Ammonia (mg/dL)	1.401	0.02*	4.060	1.243	13.257

DISCUSSION

The current study revealed high prevalence of MHE among compensated cirrhosis patients (36.7 percent). Different studies found that the prevalence of MHE in cirrhosis patients was measured at 18.2%, 30, 55.8% and 84% [18-21] based on the diagnostic criteria and the population being tested. The prevalence of MHE in patients with cirrhosis was 44.0 percent, lower than that found by Maric et al., who reported 80 percent frequency in the same patient type, according to the results of this study [22]. This discrepancy in the number of MHE patients can be attributed to variation in patient selection criteria, disparity in diagnostic criteria and variations of the measures used.

The prevalence of MHE in a previous Japanese study was 28.6% [23]. Former Egyptian studies reported that MHE was prevalent in 25.7 and 47% of patients with cirrhosis [24-25]. There were no differences between the MHE-positive and MHE-negative patients in clinical features. Elevated levels of ammonia in plasma (P=0.034) among biochemical parameters. Nevertheless, univariate and multivariate analysis showed the degree of ammonia (odds ratio, 1.023 and 1.031, respectively; confidence interval of 95 percent of coefficient figures, 1.005-1.041 and 1.006-1.058, respectively) was the only important independent indicator for detecting MHE [23].

In Awad et al., study, In terms of age and marital status, there was a statistically significant difference between normal and abnormal hepatic encephalopathy scores. There were, however, no statistically significant differences in the other descriptive data between the two groups [24]. This is in agreement with former study [26] Who has reported that age can influence neuropsychological output in MHE patients. Many studies have shown no effect of age or gender on MHE diagnosis [27].

Throughout our research we found that in patients with MHE the ammonia level was significantly higher. Such reports correlated with Gad et al. [25] and Awad et al. [24]. Nonetheless, these findings were not in line with Li et al. [28] who stated that MHE was not associated with levels of venous ammonia which can be clarified in patients with MHE, The blood-brain barrier may be breached, allowing ammonia to spread more freely across the blood-brain barrier into the brain, as the concentration of venous ammonia in MHE patients may be similar to those without MHE [30].

In the study by Awad et al., [24], they reported that smoking and increasing age, were risk factors for MHE. Gad et al.,[25] who identified smoking as a significant risk factor for MHE, too. Our result showed non-significant relation between presence of MHE and either education, marital status, AT, AST levels, total bilirubin yet with significant relation between it and both INR and ammonia level in agreement with the study by Abdelrahman et al., [30]

Hyperammonemia has been classically known to be the the main trigger of HE. Nonetheless, the role of systemic inflammatory response has increased in importance in recent years as synergistic factors, particularly TNFα andIL-6. Both are spurred by resistance to insulin and DM. In addition, DM may increase constipation risk for HE and increased glutaminase activity. Nonetheless, the safest and most effective treatment for diabetes in cirrhotics is still uncertain. Strict regulation of glucose in cirrhotic patients in general, especially in high-risk conditions of insulin resistance such as T2DM and obesity, would therefore be advised to avoid HE [18]. In an earlier study of the social consequences of cognitive disorders in minimal hepatic encephalopathy (MHE) of 60 patients with chronic genotype 1 hepatitis C and the possibilities of their L-

ornithine-L-aspartate (LOLA, Hepa-Merz) pharmacological adjustment. Fractional therapy of L-ornithine-L-aspartate (LOLA) results in a reduction in ammonium ion content in the blood and, subsequently, an increase in psychometric test results and a decrease in traffic code violation frequency. The outcome obtained will affect the reduction in the accident rate [31].

In our study, spontaneous Porto systemic shunts were detected in 65% of patients (39 cases) by doppler ultrasound at different sites in contrast to 35% (21 cases) of absent shunts at any site. In comparison to the other similar studies, Simón-Talero et al., [32] found that the prevalence of these shunts is About 60% in patients with cirrhosis.

Although, comparing to another large, multicentric, international study Bossen et al., [33] found that the prevalence of these shunts were about 56% in cirrhotics.

Nicoletti et al., [35] found that 18% of non-cirrhotic portal hypertension had at least one documented episode of overt hepatic encephalopoathy in comparison to only 14% of cirrhotics. The presence of large portosystemic shunts was the only factor significantly correlated to cognitive impairment in non-cirrhotic portal hypertensive patients.

On the other hand, our study shows elevated ammonia level in a significant percentage of our patients 88.3% in comparison to 11.6% of normal ammonia level, with mean ammonia level 63.5±10.2.

Concerning minimal hepatic encephalopathy per say, our results is comparable to Zhang Y et al., [35] results, who found that ammonia level was significantly high in patients with MHE . Although our results go with what has been reported by Iwasa et al., [36] who found that hyperammonemia is a major contributing factor to the development of covert hepatic encephalopathy (MHE&1st grade of overt HE) in cirrhotic patients.

Being cross sectional study, it only suggests risk factors but cannot really prove causal relation or time needed for any risk to head the MHE. We recommend large scale prospective studies to identify risk factors of MHE.

CONCLUSION

MHE is a prevalent condition among patients with compensated cirrhosis with high ammonia level is a strong risk factors for its development.

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