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Prevalence and Risk Factors of Minimal Hepatic Encephalopathy in Patients with Compensated Liver Cirrhosis

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ABSTRACT

Background: Minimal hepatic encephalopathy (MHE) is the earliest phase of hepatic encephalopathy. It is associated with increased risk of falls, impaired work and diminished quality of life.

Subjects and methods: This study included 302 patients with liver cirrhosis, of which 130 patients had Child A (compensated) liver cirrhosis. All patients were assessed by history taking, clinical examination, routine investigations, serum ammonia level and abdominal ultrasound for porto-systemic shunt (PSS). MHE was diagnosed in 60 patients of compensated liver cirrhosis patients using mini-mental state examination (MMSE) and number connection test A (NCT-A).

Results: Our stud showed that Child A patients were 43% of the study group and MHE was present in 46% of compensated liver cirrhosis patients. Our results showed a significant association between lower serum albumin, higher INR, high serum ammonia, presence of PSS in ultrasound examination and MMSE and NCT-A high scores with the development of MHE. MMSE and NCT A showed significantly good performance in diagnosis of MHE. Multiple regression analysis showed that high serum ammonia level (53-61) u/dl, large PSS (> 8 mm in diameter), MMSE score (22-26) and NCT A score (45-56) were the most significant risk factors for MHE.

Conclusion: MHE is a major and prevalent manifestation in compensated liver cirrhosis patients. It is associated with significant decrease in work and driving abilities and quality of life. Its major risk factors are high serum ammonia, large PSS and high scores of MMSE and NCT A tests that have a good performance in MHE diagnosis.

Keywords: Minimal hepatic encephalopathy, hepatitis C, cirrhosis, mini-mental state examination, porto-systemic shunt, number connection test A.

INTRODUCTION

Liver cirrhosis is a major global health burden affecting about 2% of the global population. Viral hepatitis (hepatitis C and B), chronic alcohol abuse and non-alcoholic steatohepatitis (NASH) are the most common causes of liver cirrhosis worldwide. Liver cirrhosis is the most common indication of liver transplantation. Despite healthcare improvements in the last few decades, Egypt still has the highest mortality rate of liver cirrhosis (72%) and 20% of deaths in adult Egyptian males between 45-55 years were due to liver cirrhosis in 2010 [(1)].

Hepatic encephalopathy is a major clinical feature of decompensated liver cirrhosis. It is a neuropsychiatric syndrome characterized by mental state and sleep disorders with or without motor manifestations. Mental state disorders range from mild cognitive impairment to deep coma [(2)].

Minimal hepatic encephalopathy (MHE) is the mildest stage of hepatic encephalopathy that affects 30-80% of patients with liver cirrhosis and often undiagnosed and untreated by physicians due to its covert nature. It is characterized by subtle changes in neuropsychological features, cognitive functions particularly in the domains of attention, vigilance and integrative function, changes in cerebral blood flow, cerebral neurotransmitters and fluid homeostasis. These covert abnormalities can't be identified by history or clinical neurological examination. However, they can be elucidated by neuropsychometric and neurophysiological tests [(3)].

MHE can be diagnosed in chronic liver disease patients with or without portosystemic shunt (PSS), and also in PSS patients due to portal hypertension without liver disease [(4)].

MHE has a substantial burden on the psychosocial and medical aspects of the patients. It interferes with and markedly diminishes the patients working ability, independent survival and quality of life especially for patients whose jobs require physical coordination. MHE is associated with impaired cognitive functions such as attention, alertness, orientation and learning processes with poor navigation and driving performance leading to high incidence of motor vehicle accidents and falls [(5)].

MHE is diagnosed in patients with grade 0 hepatic encephalopathy according to West Haven criteria if other neurophysiological/ neuropsychometric tests, as mini-mental state examination (MMSE), number connection tests, block design, digit symbol, critical

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flicker frequency and/or inhibitory control tests, confirmed the diagnosis of cognitive impairment [6].

There are some variables that may affect the interpretation of these neuropsychological/psychometric tests including the patients' age, gender, educational level, sociodemographic differences, clinical comorbidities and psychiatric disorders. Moreover, the cutoff points of these tests are population, age and education-dependent [7].

SUBJECTS AND METHODS

This is a prospective study conducted in Zagazig University Hospitals from August 2016 till June 2018. The study included 302 patients with liver cirrhosis. One-hundred and thirty patients had compensated liver cirrhosis, of which 60 patients fulfilled the criteria of minimal hepatic encephalopathy. Inclusion criteria were age ≥ 18 years old, Child score A and absence of HCC. Exclusion criteria included history of overt hepatic encephalopathy, decompensated cirrhotic patients (Child score B or C), presence of HCC, history of gastrointestinal bleeding in the previous 2 weeks, history of interferon therapy, alcohol intake, illicit drugs use, chronic obstructive pulmonary disease, psychiatric disease, hypo-or hyperthyroidism, renal insufficiency.

All patients were subjected to thorough history taking and clinical examination for features of vascular or cellular decompensation of liver cirrhosis such as jaundice, bleeding tendency, feter hepaticus, palmar erythema, spider nevi, hepatosplenomegaly, ascites and lower limb oedema.

Investigations included complete blood count (CBC), liver functions tests, kidney function tests, coagulation profile, viral markers for hepatitis B and C, serum ammonia level, fasting blood glucose level, serum electrolytes (sodium and potassium) in addition to abdominal ultrasound with Doppler to evaluate for size or masses in liver and spleen, ascites and portal vein diameter.

Child score was calculated for all patients. All patients with compensated liver cirrhosis (Child A) were also assessed by mini-mental state examination test (MMSE), a brief 30-point psychoneurological test [8].

All patients with compensated liver cirrhosis were assessed by number connection test A (NCT-A). If the patient needed more 45 seconds, MHE can be diagnosed with high sensitivity [10].

Patients with compensated cirrhosis (Child score A), MMSE score 20-26 and NCT-A more than 45 seconds, were considered to have MHE and were enrolled in our study.

Ethical approval:

All patients gave written informed consents to participate in the study. **The study protocol Conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethical Committee of Zagazig University Hospitals and Zagazig University Institutional Review Board (IRB).**

Statistical analysis:

It was done using statistical package for the social sciences (SPSS) version 18. Quantitative variables were presented as mean ± standard deviation (SD) and range. Qualitative variables were presented as frequency and percentage. Chi-square test or Fishers' Exact test was used for qualitative variables and the Student *t*-test, Mann-Whitney test and regression analysis for quantitative variables. P-value less than 0.05 was considered statistically significant.

RESULTS

Our study included 302 cirrhotic patients with 130 patients classified as Child A. Sixty patients had MHE according to our criteria. Patients with compensated liver cirrhosis & MHE had mean age 50 years, 65% were males, 77% were smokers, 73% were diabetics & increased serum ammonia level was detected in 88% of patients. Univariate analysis showed that lower serum albumin, presence of portosystemic shunts (≥ 8 mm in diameter) by Doppler US, hyperammonemia, higher mini-mental state examination and number connection test A scores were the most significant predictors of MHE as shown in tables (1 & 2). All MHE patients with serum hyperammonemia (88.3%) have detectable portosystemic shunts by Doppler ultrasonography at different sites, while none of those patients with normal ammonia level (11.6%) had detectable shunts, as shown in table (3).

MMSE had a statistically significant good performance in MHE patients compared to patients without MHE as in figure (1). Multiple regression analysis (table 4) showed that the most probable risk factors of MHE in patients with compensated cirrhosis were serum ammonia level (53-61 u/dl), large PSS > 8 mm in diameter, MMSE score 22-26 and NCT A score (45-56) seconds.

Table (1): Demographic data & Univariate analysis of the studied patient

Patient characteristics	With MHE (N.=60)	Without MHE (N.=70)	P. value
Age	49.8 ±8.4	48.3 ± 6.2	0.245
Sex (males/females) (%)	65/35	66/34	0.905
Smoking (%)	76.7	65.9	0.178
HB (gm %)	12.4 ± 1.7	12.6±2.1	0.556
Diabetes mellitus (%)	73.3	62.7	0.199
Serum bilirubin	0.8 ± 0.2	0.7±0.2	0.081
Serum albumin	3.8 ± 0.3	4.1 ± 0.5	**0.0001**
Serum Na	136.9 ± 5.7	137.4±3.5	0.541
Serum K	4.4 ± 0.6	4.2 ± 0.9	0.146
Hyperammonemia (%)	88.3	36.8	< **0.0001**
PSS by Doppler US (%)	65	22	< **0.0001**
MMSE	22.5 ± 1.8	16.7± 2.6	**0.0001**

Table 2: Mann-Whitney Test for the study groups:

Patient criteria	With MHE (N.= 60)	Without MHE (%) (N.=70)	Z-score	p. value	U- value
Platelet count	205.8 ± 44.8	193.5 ± 7.4	0.72	0.48	40
ALT	42.3 ± 8.7	38±2.3	0.34	0.73	45
Serum bilirubin	0.8 ± 0.2	0.7±0.2	0.52	0.6	9.5
INR	1.1 ± 0.2	1.3 ± 0.2	0.72	0.47	13
NCT-A	77.5 ± 3	25.6 ± 4.5	3.84	**0.0001**	**0**

Table (3): Relation between high ammonia level and the presence of portosystemic shunts in MHE patients:

Ammonia level	Porto systemic shunt				P-Value
	absent		present		
	N	%	N	%	
Normal	7	33.3	0	0	
High	14	66.7	39	100	< 0.001

Table (4): Multiple regression analysis of the studied patients

Patients characteristics	With MHE (%) (N.= 60)	Without MHE (%) (N.=70)	p. value
Serum ammonia level (53-61 umol/l)	71.6	8.6	< **0.0001**
PSS diameter (> 8 mm)	48.3	22.9	**0.003**
MMSE score (22-26)	76.7	None	< **0.0001**
NCT-A score (45-56)	63.3	None	< **0.0001**

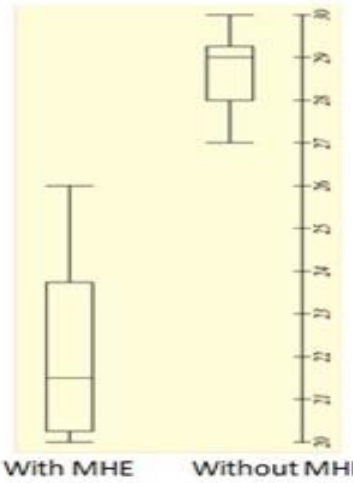

Figure 1: Performance of MMSE test in patients with and without MHE

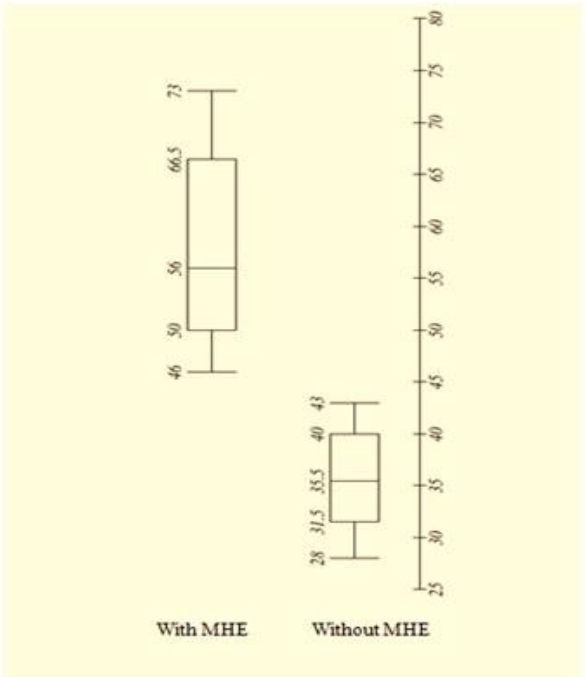

Figure 2: Performance of NCA test in patients with and without MHE

DISCUSSION

MHE, which is the earliest phase of hepatic encephalopathy, is characterized by mild neurocognitive impairment encompassing neuropsychological and neurophysiological alterations not detectable by clinical examination. It affects up to 80% of patients with cirrhosis and non-cirrhotic patients with PSS [(11)].

The neurocognitive domains more commonly affected in MHE are the attention, the visuospatial abilities, memory performance and the fine motor skills [(12)].

MHE has a negative impact on daily life activities and working capacity, health-related quality of life, impairs fitness to drive, is associated with motor vehicle crashes and predisposes the patients to fall. Furthermore, MHE is of prognostic significance as it is a risk factor for the development of overt HE [(13)].

Early diagnosis and management of MHE and its risk factors can improve cognitive functions and quality of life and avert progression to overt HE [(14)] .

Our prospective study was conducted on 302 patients with liver cirrhosis, of which 130 patients (43%) had Child A score. Sixty patients of the compensated liver cirrhosis patients (46%) had the criteria for MHE.

Most of the MHE patients (95%) had HCV-

related liver cirrhosis, which is consistent with the relatively high prevalence of HCV in Egypt (8%) reported by ***Waked et al.*** [15].

In our study, spontaneous PSS was detected in 65% of patients (39 cases) by Doppler ultrasound at different sites. This is comparable to the results of ***Simón-Talero et al.*** who reported PSS in 60% of patients with different grades of liver cirrhosis and hepatic encephalopathy. Despite the different prevalence of PSS from 42% in patients with Model of End stage Liver Disease (MELD) score of 6-9 to 72% in patients with MELD score ≥ 14, it was concluded that the presence of these shunts is significantly related to the development of HE and its chronicity [16].

Our study showed a significant increase of plasma ammonia level in 88% of MHE patients with mean ammonia level 63.5±10.2 u/dl. These results are similar to those of ***Iwasa et al. and Zhang et al***. [17, 18].

Our results showed that hyperammonemia (53-61) u/dl, presence of large PSS > 8 mm in diameter, MMSE score (22-26) and NCT A score (45-56) are the most probable risk factors for development of MHE in patients with compensated liver cirrhosis. This goes in agreement with the studies of ***Tarantino et al., Kappus et al. and Zhan et al.*** [19, 20, 21].

In conclusion; MHE is a prevalent cognitive disorder in patients with compensated liver cirrhosis that significantly impairs the quality of life, work and driving ability of these patients. The most probable risk factors predisposing to this condition are hyperammonemia and large PSS. It can be easily predicted by simple neuropsychometric and neurophysiological tests as MMSE and NCT A.

Declarations of interest: none.

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