

The effect of small intestinal bacterial overgrowth on minimal hepatic encephalopathy in patients with cirrhosis

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Abstract

Introduction: The aim of the study was to investigate the significance of factors associated with minimal hepatic encephalopathy (MHE) in cirrhotic patients.

Material and methods: Between September 2012 and August 2013, 60 cirrhotic patients, including MHE and non-MHE (NMHE) patients, were included in the study. Associated factors and clinical factors were analyzed to see if they were significantly different between MHE and non-MHE patients. Upon identifying the factors showing differences, we applied multivariate regression analysis to further decide which were the most significant ones to differentiate MHE from NMHE patients.

Results: There were 26 patients diagnosed with MHE and 34 with NMHE. Our results demonstrated that the prevalence rate of small intestinal bacterial overgrowth (SIBO) was highly associated with patients with MHE (65.4%, 17 out of 26), in contrast to the rate in NMHE patients (8.8%, 3 out of 34). We also found that factors including age, education level, intelligent test results, plasma albumin level and plasma ammonia levels were significantly different between MHE and NMHE patients. Ultimately, with logistic regression analysis, we found that SIBO was the most significant factor differentiating MHE patients from NMHE patients ($p < 0.05$).

Conclusions: In cirrhotic patients, SIBO was highly associated with MHE. This may further our understanding of the mechanisms of MHE and help to develop potential therapeutic interventions to treat cirrhotic patients with MHE.

Key words: small intestinal bacterial overgrowth, minimal hepatic encephalopathy, multivariate regression analysis.

Introduction

Hepatic encephalopathy (HE) is a severe condition of liver cirrhosis that includes a series of neurologic and neuropsychiatric complications [1, 2]. Minimal HE (MHE) is the mildest form of HE. It may happen to certain patients with chronic liver disease without obvious symptoms of hepatic encephalopathy. However, clinical manifestations and biochemical abnormalities could be detected with a fine intelligence test or comprehensive neurophysiological examination [3]. Studies have shown that patients with MHE had significant difficulties in various aspects of their lives, including social activities, emotions, sleep and work [4–6]. Thus, early detection and treatment of MHE, especially among cirrhotic patients, bear significant implications for the clinical and research societies [7, 8].

In the present study, we examined clinical factors and associations between MHE and non-MHE (NMHE) cirrhotic patients. We also applied multivariate regression analysis to determine the most significant factors that can differentiate MHE patients from NMHE patients. The purpose of the study was to further our understanding of the mechanisms of MHE and seek potential therapeutic methods to treat MHE in patients with cirrhosis.

Material and methods

Patients

Between September 2012 and August 2013, there were 60 cirrhotic patients enrolled in our department, 46 males and 14 females, aged between 36 and 68 years, with a mean age of 48.9 ± 9.74 years. All patients signed the consent forms. All experimental and clinical procedures were reviewed and approved by the Ethics Committee at the Wei Fang People's Hospital. For educational levels, all patients held high school diplomas or received a higher education. There were 54 cases of hepatitis B cirrhosis, 2 cases of hepatitis C cirrhosis and 4 cases of alcoholic cirrhosis. Based on the Child-Pugh classification, there were 21 cases of Child-Pugh grade A, 26 cases of grade B and 13 cases of grade C.

Patients were included in the study if they had not been using any antibiotics, lactulose, antacids, or other drugs affecting gastrointestinal motility in the past 2–4 weeks; had no diarrhea, abdominal pain, bloating or other symptoms; had not used any prednisone, antidepressants, opioids or other drugs before; had no recent history of severe cardiopulmonary disease, renal insufficiency, diabetes, adverse gastrointestinal diseases or extrahepatic disease caused by chronic diarrhea; had no previous history of abdominal surgery, spontaneous bacterial peritonitis or other sorts of infections. Patients with hearing or vision difficulties, or poor education, were also excluded from the study.

Diagnosis of minimal hepatic encephalopathy

The patients were tested with combined intelligence tests, including number connection test A (NCT-A), number connection test BC (NCT-BC) and the digit symbol test (DST) [9]. The definition of MHE was based on psychometric test results that were two SD more than normal on at least two psychometric tests [3].

Glucose hydrogen breath test

The detection of small intestinal bacterial overgrowth (SIBO) was conducted by the glucose

hydrogen breath test (GHBT). Briefly, it was performed after an overnight fast, beginning between 7:00 and 9:00 AM. Each patient received 1 g per kg body weight D-glucose (Merck AG, Darmstadt, Germany). Following three tries, breath samples (50 ml) were retrieved after the initial 300 ml of exhaled air. Breath samples were then collected before, and every 30 min during the 3-hour period after the intake of glucose. If the breath H_2 level rose above baseline by at least 12 ppm, it was determined to be a case of bacterial overgrowth.

Ammonia detection

The peripheral venous blood (3 ml) was taken from each patient in the morning after overnight fasting and at least one day of a low protein diet. The reference value of plasma ammonia concentration was between 11.2 and 55.3 $\mu\text{mol/l}$.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 software. The data were presented as mean \pm standard deviations. For univariate analysis on qualitative data, the χ^2 test was used. For quantitative data, the *t* test was used. For multivariable analysis, logistic regression analysis was used. Statistical significance was determined if $p < 0.05$.

Results

Small intestinal bacterial overgrowth was highly associated with minimal hepatic encephalopathy

After combined intelligence tests, 26 out of 60 patients were diagnosed with MHE. We then compared the associated factors between MHE and NMHE patients (Table I). Our results showed that there were no differences among factors such as gender, causes of disease or Child-Pugh classification between the two groups. Interestingly, the results showed that the prevalence rate of SIBO was very high in patients with MHE (65.4%, 17 out of 26), whereas the prevalence rate of SIBO was low in NMHE patients (9.7%, 3 out of 34). Statistical analysis demonstrated that the difference in SIBO prevalence rate between MHE and NMHE patients was significant ($p < 0.01$, Table I). Thus, our results demonstrated that the occurrence of SIBO was highly associated with MHE.

Some of the clinical factors were highly associated with minimal hepatic encephalopathy

In order to closely examine the mechanisms of the high prevalence rate of SIBO in MHE patients, we next compared the clinical factors between patients with MHE and NMHE patients (Table II). We

Table I. Associated factors among MHE and NMHE patients. Small intestinal bacterial overgrowth (SIBO) was highly associated with patients with MHE ($p < 0.01$)

Associated factors		MHE (n = 26)	NMHE (n = 34)	Value of p
Gender	Male	19	27	0.56
	Female	7	7	
Cause of disease	Known	23	31	0.73
	Unknown	3	3	
Child-Pugh classification	A + B	19	28	0.39
	C	7	6	
Esophageal varices	Positive	20	27	0.81
	Negative	6	7	
Ascites	Positive	11	12	0.58
	Negative	15	22	
SIBO	Positive	17	3	< 0.01
	Negative	9	31	

Table II. Comparison of clinical factors between MHE and NMHE patients. NCT-A, number connection test A. NCT-BC, number connection test BC

Clinical factors	MHE (n = 26)		NMHE (n = 34)		Value of t	Value of p
	Mean	SD	Mean	SD		
Age [years]	51.3	9.2	46.1	8.9	2.21	0.03
Education [years]	10.5	3.4	13.8	4.2	3.26	< 0.01
NCT-A	68.4	9.6	53.6	4.8	7.03	< 0.01
NCT-BC	60.7	6.5	50.2	4.4	7.47	< 0.01
Total bilirubin [$\mu\text{mol/l}$]	14.2	3.2	12.7	3.7	1.64	0.10
Direct bilirubin [$\mu\text{mol/l}$]	10.3	4.5	9.2	3.9	1.01	0.31
Plasma albumin [g/l]	37.5	7.4	42.0	9.4	2.14	0.03
PT [s]	11.1	3.5	13.1	3.7	2.12	0.03
Plasma ammonia [$\mu\text{mol/l}$]	48.7	8.8	34.9	7.5	6.55	< 0.01
Child score	7.48	2.7	6.37	2.6	1.61	0.11

found that there were no differences in total bilirubin or direct bilirubin between MHE and NMHE patients. However, some of the factors, such as age, education levels, intelligent test results, plasma albumin level and plasma ammonia levels, were significantly different between MHE patients and NMHE patients.

Small intestinal bacterial overgrowth was the most significant factor in patients with minimal hepatic encephalopathy

Since we discovered that several associated factors and clinical factors were significantly different between MHE and NMHE patients, we ap-

plied multivariate logistic regression analysis to examine which factor was the most significant one to differentiate MHE patients from NMHE patients. Our results showed that SIBO was the most significant factor among MHE patients (Table III).

Discussion

The likelihood of cirrhotic patients developing MHE is very high. Globally, the prevalence rate of MHE among cirrhotic patients ranges from 30% to 90% [10–13], and the estimated level is well above 50% in Chinese patients [14]. The major finding of the present study is that SIBO was more prevalent in cirrhotic patients with MHE than the

Table III. Multivariate logistic regression analysis showed that SIBO was the most significant factor among MHE patients

Variables	Odds ratio	95% CI		Value of <i>p</i>
		Lower	Upper	
Age	1.14	1.07	1.26	< 0.001
Education level	0.51	0.41	0.62	< 0.001
Plasma albumin	1.12	0.80	1.58	0.02
Plasma ammonia	1.24	1.13	1.36	< 0.001
SIBO	1.36	1.22	1.51	< 0.001

patients without MHE. The percentage of cirrhotic patients with MHE in our study was 43.3%, similar to previous studies [15–17].

We demonstrated, in the present study, that other clinical factors were also associated with MHE, such as age [18], plasma albumin [19], or the possibility of developing overt encephalopathy [20]. The MHE patients had higher levels of intestinal bacteria and plasma ammonia, as compared with NMHE patients. Previous studies showed that the prevalence of intestinal bacterial overgrowth was very high, and correlated with bacterial DNA translocation in patients with cirrhosis [21, 22]. This is consistent with our results showing that in MHE patients the prevalence rate of SIBO was dramatically unregulated as Child-Pugh scores increased. Thus, it is very likely that SIBO actively led to severe deterioration of liver function.

There are several limits worth noting in the current study. First, the patients included in the current study were mostly diagnosed with hepatitis B cirrhosis. While both hepatitis B and hepatitis C viruses are common causes of cirrhosis, the possible explanation for the unbalanced sampling in the present study would be that the Chinese population (or Asian-Pacific population) in particular is more likely to develop hepatitis B than hepatitis C [23, 24]. Further study with a larger sample size of western cirrhotic patients would help us gain more insights into the relationship between SIBO and MHE. Second, the diagnostic method for SIBO in the present study was GHBT, instead of the gold standard of culture. We used GHBT as it was easy to perform and the results were quickly available to the physicians. However, it is possible to get negative GHBT results in patients with SIBO as the glucose in the distal part of the intestinal ducts was already digested. Other tests, such as endoscopy and quantitative cultures, would be more accurate and thus complementary to GHBT for diagnosing SIBO in patients. Finally, we did not conduct extensive research on the correlation of other factors with SIBO in affecting MHE in cirrhotic patients. For example, studies showed that plasma ammonia

was an important factor to determine the inflammation in MHE patients, and improving the micro-environment could substantially help MHE patients to achieve better neuropsychological functions [25, 26]. Future study would be needed to further explore the associations of SIBO with other factors, including plasma ammonia, in the diagnosis and treatment of cirrhotic patients with MHE.

In conclusion, our results clearly demonstrated that in cirrhotic patients SIBO was highly associated with MHE. This information would undoubtedly further our understanding on the mechanisms of SIBO development and its direct effect on development of MHE in cirrhotic patients. Moreover, it may help to develop early diagnostic methods and potential therapeutic interventions targeting SIBO to treat HE patients.

Conflict of interest

The authors declare no conflict of interest.

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