

## Original Article

# Effects of SIBO and rifaximin therapy on MHE caused by hepatic cirrhosis

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**Abstract:** Aim: To determine the effects of small-intestinal bacterial overgrowth (SIBO) and rifaximin therapy on minimal hepatic encephalopathy (MHE) with liver cirrhosis. Methods: A total of 60 patients with cirrhosis were included in this study. Patients were evaluated by three neuropsychometric tests including number connection-A (NCT-A), number connection-BC (NCT-BC) and digit symbol test (DST) to diagnose the MHE. Glucose breath testing was used to determine the presence of SIBO. Patients with MHE were then treated with 200 mg of rifaximin orally three times a day for a week. Glucose breath testing and psychometric tests were repeated upon 4 weeks after antibiotic completion. Blood ammonia levels were also monitored before and after rifaximin treatment. Results: Of the 60 patients enrolled, 26 were diagnosed with MHE. The mean blood ammonium level in MHE group was  $48.7 \pm 8.8 \mu\text{mol/L}$ , while in non-MHE it was  $34.9 \pm 7.5 \mu\text{mol/L}$ , demonstrating an increase ( $t = 6.55$ ,  $P < 0.05$ ). One third of patients had an abnormal glucose hydrogen breath test, indicating the presence of SIBO. Abnormal breath test results were present in 3 of the 34 patients (8%) without MHE, 17 of the 26 patients (65.4%) with MHE. One week after rifaximin antibiotic therapy, the number of the MHE patients reduced from 26 to 11. Among 17 MHE patients with SIBO, 13 became SIBO negative. Blood ammonium level in MHE patients with SIBO decreased from  $51.6 \pm 5.4 \mu\text{mol/L}$  to  $39.1 \pm 7.6 \mu\text{mol/L}$  ( $P < 0.01$ ), while in MHE patients without SIBO decreased from  $45.3 \pm 9.8 \mu\text{mol/L}$  to  $36.9 \pm 8.8 \mu\text{mol/L}$  ( $P < 0.01$ ). Higher reduction was observed in SIBO group. All three psychometric test results showed significant ( $P < 0.01$ ) improvement after rifaximin treatment. Conclusions: SIBO is prevalent in MHE patients with liver cirrhosis, and short-term treatment with rifaximin can effectively reduce blood ammonia level and improve psychometric test.

**Keywords:** Minimal hepatic encephalopathy, neuropsychometric test, small-intestinal bacterial overgrowth, rifaximin

## Introduction

Small-intestinal bacterial overgrowth (SIBO) has been reported to be prevalent in patients with cirrhosis due to impaired intestinal motility associated with altered autonomic function. Its frequency of the occurrence was related to the severity of the liver disease [1]. Intestinal bacteria which produce ammonia as neurological toxin play an important role in the development of hepatic encephalopathy (HE), a neuropsychiatric and neurocognitive complication which may result in serious consequences for patient with cirrhosis [2]. Minimal hepatic encephalopathy (MHE) is the mildest form of hepatic encephalopathy (HE), which is defined as hepatic encephalopathy without manifesting obvious clinical symptoms and biochemical abnor-

malities, but the intellectual, neural or mental abnormality can be diagnosed by specific neuropsychological or neuro-electrophysiological testing.

Based on the findings on the relation between SIBO and MHE, the alteration of intestinal microecology has been a common treatment strategy for MHE. The non-absorbable sugar lactulose therapy has been the standard treatment for patients with HE. But its effectiveness in treating HE has been contradictory [3-5], and its adverse effect is also a concern [6]. In recent years, non-absorbable antibiotic rifaximin has gained attention for the treatment of HE. Rifaximin is a broad-spectrum nonsystemic antibiotic. The majority of the drug concentrates in the gastrointestinal tract [7], and it has previ-

**Table 1.** Blood ammonium level changes in MHE patients before and after rifaximin treatment

Blood ammonium concentration ( $\mu\text{mol/L}$ )			Cases	t	P
	Pre-treatment	Post-treatment			
With SIBO	$51.6 \pm 5.4$	$39.1 \pm 7.6$	17	4.87	$< 0.01$
Without SIBO	$45.3 \pm 9.8$	$36.9 \pm 8.8$	9	2.14	0.04

*SIBO test*

Glucose hydrogen breath test (GHBT) was used to identify abnormal growth of bacteria in the intestine. SIBO is diagnosed if there is a rise in breath hydrogen by 12 ppm above the basal level after glucose ingestion.

ously been shown to be effective in the treatment of HE [8].

In this study we examined the effects of SIBO and rifaximin antibiotic therapy on MHE patients by monitoring blood ammonia levels and neuropsychological changes before and after the antibiotic treatment.

**Materials and methods***Study subjects*

The study subjects included 60 liver cirrhosis patients admitted to our hospital between Sep 2006 and Aug 2012. There were 46 males and 14 females. The ages of patients were between 36 to 68-year-old, with mean age of  $48.9 \pm 9.74$ . Patient's education levels were middle school or higher. The 60 patients with liver cirrhosis consisted of 54 hepatitis B related cirrhosis, 2 hepatitis C related cirrhosis and 4 alcoholic cirrhosis. The degree of severity based on Child Pugh Criteria demonstrated 21 level A, 26 level B and 13 level C. Forty healthy volunteers were recruited to serve as controls.

Patient exclusion criteria included: (1) use of antibiotics, lactulose, antacid or any drugs known to affect gastro-intestinal motility within the previous 2 to 4 weeks; (2) diarrhea, stomachache or abdominal distention; (3) use of drugs such as prednisone, antidepressant and opiates; (4) diseases that can cause poor gastrointestinal motility such as cardiac and pulmonary dysfunction, renal insufficiency or diabetes; (5) chronic diarrhea or malabsorption caused by concomitant extrahepatic diseases; (6) history of gastrointestinal tract or abdominal surgery; (7) spontaneous peritonitis or other severe infections; (8) colonoscopy or enema treatment within 4 weeks; (9) hepatic encephalopathy with clinical signs (10) inability to complete test (NCT) and symbol digit test (SDT) due to hearing loss, poor vision, etc.; (11) illiterate or poor compliant patients.

*Diagnosis of MHE*

All patients and controls underwent a series of psychometric test including number connection-A (NCT-A), number connection-BC (NCT-BC) and digit symbol test (DST) administered by a trained personnel. Compared to age matched controls, time greater than two SD from the mean for the NCT, score less than two SD from the mean for the DST were considered abnormal. Patients with abnormal results from 2 or more psychometric tests were diagnosed with MHE.

Glucose breath testing Three ml of peripheral venous blood samples were collected in the early morning after fast from all the research subjects and sent to the clinical lab for ammonia test. Individuals were required to take low-protein diet from the day before the blood collection. The normal range should be: 11.2-55.3  $\mu\text{mol/L}$ .

*Antibiotic therapy*

MHE patients were given 200 mg of rifaximin orally three times a day for a week. SIBO, blood ammonia test, and psychometric tests were repeated upon 4 weeks after antibiotic completion.

*Statistic analysis*

SPSS 12.0 statistical software was used for the statistic analysis. The results of the two groups were compared using the  $\chi^2$  test for the enumeration data, a *t*-test for the numerical data. Spearman's rank correlation was calculated to determine correlation between two variables. The significance level ( $\alpha$ ) was set at 0.05.

**Results**

Twenty six (43.3%) patients were diagnosed to have MHE in the total 60 patients with hepatic cirrhosis. The mean blood ammonium level in MHE group was  $48.7 \pm 8.8 \mu\text{mol/L}$ , while in

**Table 2.** Psychometric test results from healthy volunteers

Age (yr)	NCT-A (second)		NCT-BC (second)		DST (score)
	middle school	College or higher	middle school	college or higher	
20-39	36.1 ± 15.4	26.5 ± 10.3	63.2 ± 21.4	40.5 ± 14.5	49.9 ± 4.7
40-59	48.8 ± 17.7	37.0 ± 11.7	83.6 ± 31.0	67.6 ± 24.9	38.5 ± 5.0
> 60	62.7 ± 30.3	45.5 ± 13.9	104.0 ± 39.3	77.8 ± 21.6	35.4 ± 4.7

**Table 3.** Neuropsychological changes from patients with MHE before and after rifaximin treatment

Test	Pre-treatment	Post-treatment	t	P
NCT-A	68.4 ± 9.6 s	53.6 ± 4.8 sec	7.03	< 0.01
NCT-BC	96.7 ± 7.9 s	83.7 ± 3.9 sec	7.52	< 0.01
DST	33.7 ± 6.5 min	45.2 ± 4.4 min	7.47	< 0.01

non-MHE it was  $34.9 \pm 7.5 \mu\text{mol/L}$ , demonstrating an increase ( $t = 6.55$ ,  $P < 0.05$ ). Seventeen patients (65.4%) were diagnosed to have SIBO in MHE group compared to 3 (8.8%) in non-MHE group ( $X^2 = 21.2$ ,  $P < 0.05$ ). As shown in **Table 1**, the average blood ammonium level in 17 MHE patients diagnosed with SIBO was  $51.6 \pm 5.4 \mu\text{mol/L}$ , while in 9 MHE patients without SIBO it was  $45.3 \pm 8.8 \mu\text{mol/L}$ . This demonstrates an increase of blood ammonia level in MHE patients with SIBO ( $t = 2.2718$ ,  $P = 0.03$ ).

All the MHE patients were treated with rifaximin for a week. As a result, the number of the MHE patients reduced from 26 to 11. This translated to a 42.3% reduction in MHE associated with rifaximin treatment. Among 17 MHE patients with SIBO, 13 became negative for bacterial overgrowth, which was confirmed by hydrogen breath test after 4 weeks. These reductions showed close correlation ( $r = 0.75$ ,  $P < 0.05$ ).

As shown in **Table 1**, after rifaximin treatment, blood ammonium level in MHE patients with SIBO decreased from  $51.6 \pm 5.4 \mu\text{mol/L}$  to  $39.1 \pm 7.6 \mu\text{mol/L}$  ( $P < 0.01$ ), while in MHE patients without SIBO decreased from  $45.3 \pm 9.8 \mu\text{mol/L}$  to  $36.9 \pm 8.8 \mu\text{mol/L}$  ( $P < 0.01$ ). Higher reduction was observed in SIBO group.

The psychometric tests results from healthy volunteers are shown in **Table 2**. **Table 3** presents the results of psychometric test in 26 MHE patients before and after rifaximin treatment, all three test results showed significant ( $P < 0.01$ ) improvement after rifaximin treatment.

## Discussions

MHE is found in 30-84% of patients with liver cirrhosis without overt hepatic encephalopathy (HE) [9]. The pathophysiological mechanisms of MHE have not been fully elucidated, but ammonia and the downstream consequences of ammonia uptake by astrocytes are reported to be central to the process [10, 11]. Multivariate analysis performed by Gupta and colleagues demonstrated that the SIBO was the only factor associated with MHE [12]. SIBO can increase blood ammonium and endotoxin, and once it occurs, it is hard to break the chain reactions from the vicious cycle of SIBO, microbial translocation and endotoxaemia [13]. Therefore, early detection and treatment of SIBO are critical for the prevention the MHE in cirrhotic patients.

In this study, we found that the prevalence of SIBO was significantly higher in cirrhotic patients with MHE (65.4%) compared to cirrhotic patient without MHE (8.8%,  $P < 0.05$ ). Similarly, the average blood ammonia level of MHE patients ( $48.7 \pm 8.8 \mu\text{mol/L}$ ) was also higher than that of non-MHE patients with cirrhosis ( $34.9 \pm 7.5 \mu\text{mol/L}$ ,  $P < 0.05$ ). For MHE patients with SIBO, their average blood ammonia level ( $51.6 \pm 5.4 \mu\text{mol/L}$ ) was higher compared to MHE patients without SIBO ( $45.3 \pm 8.8 \mu\text{mol/L}$ ,  $P = 0.03$ ), indicating that the blood ammonia plays a role in the onset and progression of MHE with SIBO.

There were 8% of non-MHE with SIBO, and 34.6% of MHE without SIBO, indicating that other factors are also involved in the MHE development besides ammonia. Some reports pointed out that it was the inflammation caused by ammonia that triggers the impairment of neuropsychological function, and plays an important role in determination of the presence and severity of MHE [10, 11]. Infection and oxidative stress are key factors and may synergistically act with ammonia [10].

The objective of antibiotic therapy in HE is to decrease the bacterial flora that produce ammonia. Historically, neomycin and metronidazole have been used in treating HE for many years, but their use has been abandoned because of the lack of efficacy and their toxicity. Rifaximin is a synthetic antibiotic designed to target GI tract pathogenic microorganisms. It has a broad spectrum of bioactivity against both Gram-positive and Gram-negative, aerobic and anaerobic bacteria with good patient tolerance and a low incidence of side effects [14]. Many data support the usage of rifaximin for the treatment of HE and SIBO [15, 16].

After treatment with rifaximin at 200 mg t.i.d. for 7 days, blood ammonia level in all MHE patients showed significant decrease, and more decrease was observed in those with SIBO. Thirteen out of 17 MHE with SIBO became SIBO negative, and their psychometric test scores also returned to normal. Our data support that the increase of blood ammonia level is caused by SIBO. The blood ammonia levels in MHE without SIBO also reduced after antibiotic therapy indicating that rifaximin treatment may improve small intestines microecology and autonomic nerve functions.

Our study demonstrates a high prevalence of SIBO in cirrhotic patients with MHE, and a single short-term course treatment with rifaximin can effectively reduce blood ammonia level and reverse the MHE symptoms.

#### Disclosure of conflict of interest

None.

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