Small Intestinal Bacterial Overgrowth Diagnosed by a Breath Test and Improved by Rifaximin in a Patient with Hepatic Encephalopathy and Alcoholic Liver Cirrhosis: A Case Report

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Abstract:
A 66-year-old Japanese man was admitted to our hospital with grade 2 hepatic encephalopathy (HE). Abdominal computed tomography and laboratory examinations revealed decompensated liver cirrhosis. Intravenous administration of branched-chain amino acids immediately ameliorated the HE, and lactulose was initiated. However, a breath test revealed small intestinal bacterial overgrowth (SIBO); therefore, rifaximin was additionally initiated. The breath test was repeated after discharge, when no evidence of SIBO or overt HE was identified. This case suggested that a breath test is effective for the identification of SIBO and that the administration of a poorly absorbed antibiotic should be considered in SIBO-positive HE patients taking lactulose.

Key words: hepatic encephalopathy, liver cirrhosis, poorly absorbed antibiotics, small intestinal bacterial overgrowth

Introduction
The prevalence of overt hepatic encephalopathy (HE) is 10%-14% in patients with liver cirrhosis (LC) (1, 2). HE is a psychoneurotic symptom that is characterized by an impaired consciousness complicated by acute or chronic severe liver dysfunction (3), which negatively affects the prognosis and quality of life (4, 5). The pathogenic mechanisms underlying HE have not been entirely elucidated; however, encephalopathy-inducing factors have been found to originate in the gut and easily flow into the portal vein in LC patients due to small intestinal bacterial overgrowth (SIBO) and leaky gut syndrome (6). Furthermore, these factors can reach the brain because of a diminished liver clearance capability and portosystemic shunt formation, where they induce psychoneurotic symptoms (7, 8).

SIBO is characterized by abnormal bacterial overgrowth in the small intestine, as the name suggests, leading to intestinal mucosal inflammation and malabsorption (9). SIBO can be complicated by various conditions, including Crohn’s disease, chronic pancreatitis, and LC (10). A systematic review showed that the prevalence of SIBO in patients with LC is 40.8% (95% confidence interval, 34.8-47.1; odds ratio, 6.83; p<0.001), and that SIBO is significantly associated with LC-related complications, such as covert HE, ascites, and spontaneous bacterial peritonitis (11). SIBO is diagnosed when there is presence of >10^5 colony-forming units/mL in the cultivation of proximal jejunal fluid (12, 13) or there is an increase of gut metabolites in the breath after sugar substrate loading (14). Dietary therapy (15) and antibiotics (16-18) have been reported to be the therapeutic options for SIBO.

We herein report the case of an HE patient with SIBO diagnosed though a breath test and the progression to overt HE was prevented by the administration of rifaximin and lactulose. To our knowledge, this is the first case report in which a breath test was used for the diagnosis of SIBO in a...
A 66-year-old Japanese man was admitted to our hospital due to frequent tottering and tumbling. He was attended to cardiovascular internal medicine and treated for sustained ventricular tachycardia, chronic atrial fibrillation, and a history of surgery for aortic valve regurgitation. He was administered several drugs, including diuretics, antihypertensives, antiarrhythmic agents, anticoagulants, hypnotics, and laxatives (presented in Table 1). He consumed Japanese sake (containing 80-100 g of ethanol) approximately every day prior to admission.

A physical examination showed a stable cardiovascular state (heart rate 69 bpm, blood pressure 102/69 mmHg, and no cardiac murmur) and no fever (36.7°C). His consciousness and attention were slightly impaired, and he had a Glasgow coma scale score of 13 points. He was slightly drowsy but showed no flapping tremor. No evidence of recent cerebrovascular accident was detected, with computed tomography of the brain showing only an old cerebral infarction. Furthermore, enhanced abdominal computed tomography showed liver atrophy and the presence of ascites but no detectable portosystemic shunt; therefore, LC was suspected.

A laboratory examination revealed hyperammonemia (234 μg/mL) with severe liver (with serum albumin of 2.4 g/dL, serum bilirubin of 2.5 mg/dL, and albumin-bilirubin grade of 3) (19) and renal dysfunction (with serum creatinine of 1.39 mg/dL and an estimated glomerular filtration rate of 40.7 mL/min/1.73 m²) (Table 2). Based on these findings, a definitive diagnosis of grade 2 HE (20) due to decompensated LC in Japan.

Table 1. Taking Drugs on Admission.

| Drug                         | Daily dosage |
|------------------------------|--------------|
| **Diuretics**                |              |
| Furosemide                   | 20mg         |
| Spironolactone               | 25mg         |
| **Antihypertensives**        |              |
| Enalapril                    | 1.25mg       |
| Carvedilol                   | 20mg         |
| **Antiarrhythmic agents**    |              |
| Bisoprolol                   | 2.5mg        |
| Sotalol                      | 80mg         |
| **Anticoagulants**           |              |
| Warfarin potassium           | 1mg          |
| **Hypnotics**                |              |
| Ramelteon                    | 8mg          |
| Etizolam                     | 2mg          |
| **Laxatives**                |              |
| Magnesium oxide              | 1g           |

Table 2. Laboratory Data on Admission.

| Hematocrit (g/dL) | 3.300-8.600 | Normal value | Biochemistry | Normal value |
|-------------------|-------------|--------------|--------------|--------------|
| Leukocyte count/mm³) | 10,970     | Total Protein(g/dL) | 7.3          | 6.6-8.1      |
| Erythrocyte count(×10³/mm³) | 334        | Albumin(g/dL) | 2.4          | 4.1-5.1      |
| Hemoglobin (g/dL) | 10.4        | Serum sodium (mEq/L) | 137          | 138-145      |
| Hematocrit (%)   | 29.4        | Serum potassium (mEq/L) | 3.8          | 3.6-4.8      |
| Platelet count(×10³/mm³) | 15.5    | Serum chloride (mEq/L) | 108          | 101-108      |
| **Tumor marker** |              | Total bilirubin (mg/dL) | 2.5          | 0.4-1.5      |
| α-fetoprotein (mg/mL) | 5          | Direct bilirubin (mg/dL) | 0.9          | <0.3         |
| **Viral marker** |              | AST (IU/L) | 181          | 13-30        |
| HBsAg negative    | negative    | ALT (IU/L) | 99           | 10-42        |
| HBeAb negative    | negative    | LDH (IU/L) | 313          | 24-222       |
| HCV-Ab negative   | negative    | ALP (IU/L) | 879          | 106-322      |
| **Immunology**    |              | GGT (IU/L) | 660          | 13-64        |
| anti-nuclear antibody | ×40      | BUN (mg/dL) | 30           | 8-20         |
| anti-mitochondrial antibody | negative | Creatinine (mg/dL) | 1.39         | 0.65-1.07    |
| Immunoglobulin G (mg/dL) | 1.611 | Serum ammonia (µL/dL) | 234          | 12-66        |
| Immunoglobulin A (mg/dL) | 652       | CRP (mg/dL) | 4.76         | <0.15        |
| Immunoglobulin M (mg/dL) | 62        | eGFR (mL/min/1.73m²) | 40.7         | >90          |
| **Coagulation test** | Prothrombin time (%) | 23*          | 70-130       |
| PT-INR            | 2.55*       | BNP (pg/mL) | 409.2        | <18.4        |

Abnormal values are given in bold type.

*Prothrombin time and PT-INR were affected by the administration of warfarin in the case.

HBsAg: hepatitis B surface antigen, HBeAb: hepatitis B core antibody, HCV-Ab: hepatitis C virus-antibody, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transpeptidase, BUN: blood urea nitrogen, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, BNP: brain natriuretic peptide, PT-INR: international normalized ratio of prothrombin time
sated LC was made. No evidence of viral or autoimmune hepatitis was noted; therefore, the LC was considered to be due to prolonged alcohol abuse.

Fig. 1 presents the clinical course of the patient. The intravenous administration of branched-chain amino acids immediately improved the HE, and the administration of oral branched-chain amino acids and lactulose, a synthetic disaccharide, was initiated. A breath test performed 14 days following his admission showed a hydrogen level of 99 ppm (a rise of 56 ppm from baseline) 30 min after glucose loading and no increase in methane (2 ppm), so small intestinal bacterial overgrowth (SIBO)-complicated liver cirrhosis was diagnosed (A). Furthermore, the breath test was repeated 68 days after discharge and showed that the SIBO had been ameliorated, with a rise of only 7 ppm from the baseline hydrogen level and a level of 1 ppm for methane during the 120 min following glucose loading (B).

The patient was discharged with symptomatic improve-
ment 23 days following admission. The breath test was repeated 68 days after discharge and showed that the SIBO had been ameliorated, with a rise of only 7 ppm from baseline in hydrogen and a level of 1 ppm for methane during the 120 minutes following glucose loading (Fig. 2B). Although overt HE was not observed, the serum ammonia level was slightly high (110 μg/mL), and the number connection test (NCT) was positive (NCT-A was 66.4 seconds and NCT-B was 97.6 seconds, according to the Japanese cut-off values) (21). These findings indicated that minimal HE was still present, so drug administration was continued. No overt HE was observed for six months following discharge.

Discussion

According to practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (20), lactulose is the first-choice treatment for overt HE, and rifaximin is an add-on therapy to lactulose for the prevention of overt HE recurrence. The efficacy of poorly absorbed antibiotics, such as rifaximin, for the treatment and prevention of HE has been previously reported (22, 23). Zhang et al., in their cohort study, showed that covert HE patients with LC were complicated with SIBO at a significantly higher rate than non-HE patients with LC. Furthermore, in covert HE patients, rifaximin significantly decreased the serum ammonia levels in patients with SIBO and improved the NCT score in patients both with and without SIBO (24). Therefore, in some cases, rifaximin ameliorated HE by modulating the composition of the intestinal gut microbiota, and breath test may be effective for the identification of good responders. In the present case, we administered rifaximin to prevent the recurrence of overt HE, as the amelioration of SIBO might help prevent this recurrence; and indeed, SIBO as assessed using the breath test was ameliorated following the administration of rifaximin.

There is no gold standard for the diagnosis of SIBO. As mentioned above, two diagnostic methods have been reported: proximal jejunal fluid cultivation and the breath test. Initially, SIBO was diagnosed by proximal jejunal fluid culture, but there are several limitations associated with this method, including the invasiveness of proximal jejunal fluid collection, the presence of nonculturable bacteria (approximately 60% of the intestinal microbiota) (25), and the possibility of oral bacterial contamination. In contrast, the breath test is easy to perform and is minimally invasive. Orally ingested sugar substrates, such as lactulose and glucose, are metabolized by gut bacteria, and their metabolites, such as hydrogen and methane, are detected in the breath.

Therefore, the breath test involves the measurement of metabolite concentrations in breath after the ingestion of sugar substrates. SIBO is diagnosed when such metabolites are rapidly detected in the breath because the sugar substrates are metabolized by the overgrown intestinal bacteria. However, the breath test method has not been standardized. In the present study, glucose was used as the sugar substrate, and hydrogen and methane were measured 120 minutes after its consumption. Methanogens are found in 10%–20% of SIBO patients, and the breath test showed low hydrogen and high methane concentrations in these cases (26). Furthermore, the following two diagnostic criteria were used, according to the North American consensus (27): a rise of ≥20 ppm from baseline in hydrogen by 90 minutes and a level of ≥10 ppm in methane. In the present case, the breath test revealed an increased level of hydrogen and not of methane and indicated bacterial overgrowth without methanogens.

In 2000, Bauer et al. (28) concluded that the glucose breath hydrogen test performed poorly in patients with LC because of the discrepancy between the breath test and proximal jejunal fluid cultivation. Sundin et al. in 2018 (29) compared the breath test, jejunal fluid cultivation, and bacterial genome equivalents of jejunal fluid and found no significant correlation of the breath test findings with the colony count, just as Bauer et al. reported (28), but did note a significant correlation with a reduced viability of jejunal bacteria. The results indicated that nonculturable bacteria were dominantly increased in breath test-positive patients, and the authors considered these bacteria to potentially have pathogenicity. In the previous systematic review (11), 85.7% (18/21) of reports used the breath test for the detection of SIBO in several countries, but not in Japan.

This case report has a limitation, as the patient started taking several agents and had a history of alcohol abuse. The efficiency to SIBO of these agents and alcohol abstinence after admission were not excluded. To assess the effects on various factors, more cases should be identified, and further analyses should be performed.

In conclusion, the assessment of SIBO should be considered in LC patients with HE. For such patients, a breath test is effective and minimally invasive. Furthermore, the add-on administration of a poorly absorbed antibiotic should be considered in SIBO-positive patients with HE taking lactulose.

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