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【 CASE REPORT 】

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

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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

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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 patient with LC in Japan.

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Case Report

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.

Table 1. Taking Drugs on Admission.

Diuretics	Daily dosage
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

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℃). 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 m^2) (Table 2). Based on these findings, a definitive diagnosis of grade 2 HE (20) due to decompensated LC was made. No evidence of viral or autoimmune

Table 2. Laboratory Data on Admission.

Hematology		Normal value	Biochemistry		Normal value
Leukocyte count(/mm^3)	**10,970**	3,300-8,600	Total Protein(g/dL)	7.3	6.6-8.1
Erythrocyte count(×10^4/mm^3)	**334**	435-555	Albumin(g/dL)	**2.4**	4.1-5.1
Hemoglobin(g/dL)	**10.4**	13.7-16.8	Serum sodium (mEq/L)	**137**	138-145
Hematocrit (%)	**29.4**	40.7-50.1	Serum potassium(mEq/L)	3.8	3.6-4.8
Platelet count(×10^4/mm^3)	**15.5**	15.8-34.8	Serum chloride(mEq/L)	108	101-108
			Total bilirubin(mg/dL)	**2.5**	0.4-1.5
Tumor marker			Direct bilirubin(mg/dL)	**0.9**	<0.3
α-fetoprotein(ng/mL)	5	<9.5	AST(IU/L)	**181**	13-30
			ALT(IU/L)	**99**	10-42
Viral marker			LDH(IU/L)	**313**	124-222
HBsAg	negative	negative	ALP(IU/L)	**879**	106-322
HBcAb	negative	negative	GGT(IU/L)	**660**	13-64
HCV-Ab	negative	negative	BUN(mg/dL)	**30**	8-20
			Creatinine(mg/dL)	**1.39**	0.65-1.07
Immunology			Serum ammonia (μL/dL)	**234**	12-66
anti-nuclear antibody	**×40**	<×40	CRP (mg/dL)	**4.76**	<0.15
anti-mitochondrial antibody	negative	negative	eGFR (mL/min/1.73m^2)	**40.7**	>90
Immunoglobulin G(mg/dL)	1,611	861-1,747	BNP (pg/mL)	**409.2**	<18.4
Immunoglobulin A(mg/dL)	**652**	93-393			
Immunoglobulin M(mg/dL)	62	33-183	**Coagulation test**		
			Prothrombin time (%)	**23***	70-130
			PT-INR	**2.55***	<1.00

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, HBcAb: 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

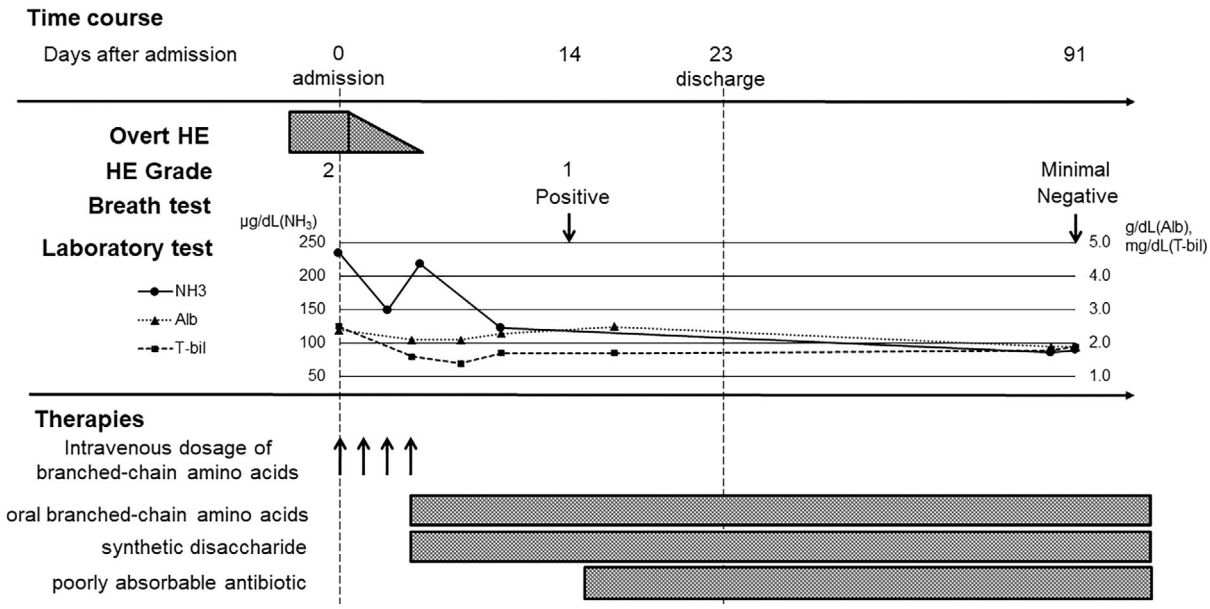

Figure 1. **Clinical course of hepatic encephalopathy, laboratory tests, and therapies. The intravenous administration of branched-chain amino acids immediately improved the HE, and the administration of oral branched-chain amino acids and lactulose, a synthetic disaccharide, was initiated. A breath test was performed 14 days following his admission; SIBO-complicated liver cirrhosis was diagnosed, and the administration of 1,200 mg/day rifaximin, a poorly absorbed antibiotic, was initiated in addition to lactulose. The patient was discharged with symptomatic improvement 23 days following admission. Furthermore, the breath test was repeated 68 days after discharge and showed that the SIBO had been ameliorated with no recurrence of overt HE. HE: hepatic encephalopathy, SIBO: small intestinal bacterial overgrowth, NH_3: ammonia, Alb: albumin, T-bil: total bilirubin**

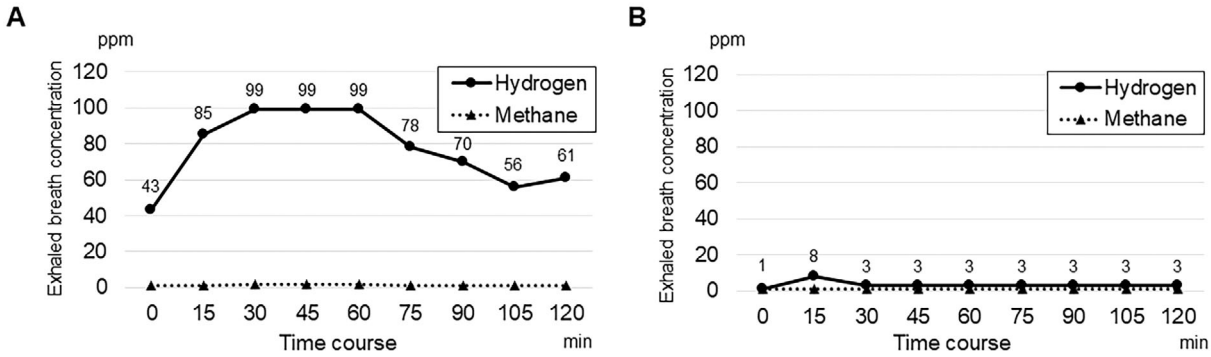

Figure 2. **The results of the breath test. A breath test performed 14 days following his admission showed a hydrogen level of 99 ppm (a rise of 56 ppm from baseline) 30 minutes after glucose loading and no increase in methane (2 ppm), so small intestinal bacterial overgrowth (SIBO)-complicated liver 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 minutes following glucose loading (B).**

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 minutes after glucose loading and no increase in methane (2 ppm) (Fig. 2A). Based on the breath test findings, SIBO-complicated LC was diagnosed, and the administration of 1,200 mg/day rifaximin, a poorly absorbed antibiotic, was initiated in addition to lactulose.

The patient was discharged with symptomatic improvement 23 days following admission. The breath test was re-

peated 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 jejunum 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.

Author's disclosure of potential Conflicts of Interest (COI).
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References

1. Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. Br Med J (Clin Res Ed) **282**: 263-266, 1981.
2. Romero-Gómez M, Boza F, García-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol **96**: 2718-2723, 2001.
3. Weissenborn K. Hepatic encephalopathy: definition, clinical grading and diagnostic principles. Drugs **79**: 5-9, 2019.
4. Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol **30**:

890-895, 1999.
5. Wijdicks EF. Hepatic encephalopathy. N Engl J Med **375**: 1660-1670, 2016.
6. Ciećko-Michalska I, Szczepanek M, Słowik A, Mach T. Pathogenesis of hepatic encephalopathy. Gastroenterol Res Pract **2012**: 642108, 2012.
7. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology **35**: 716-721, 2002.
8. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol **60**: 197-209, 2014.
9. Ghosh G, Jesudian AB. Small intestinal bacterial overgrowth in patients with cirrhosis. J Clin Exp Hepatol **9**: 257-267, 2019.
10. Choung RS, Ruff KC, Malhotra A, et al. Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture. Aliment Pharmacol Ther **33**: 1059-1067, 2011.
11. Maslennikov R, Pavlov C, Ivashkin V. Small intestinal bacterial overgrowth in cirrhosis: systematic review and meta-analysis. Hepatol Int **12**: 567-576, 2018.
12. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol **16**: 2978-2990, 2010.
13. Corazza GR, Menozzi MG, Strocchi A, et al. The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. Gastroenterology **98**: 302-309, 1990.
14. Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome and its relationship with oro-cecal transit time. Indian J Gastroenterol **25**: 6-10, 2006.
15. Vanuytsel T, Tack JF, Boeckxstaens GE. Treatment of abdominal pain in irritable bowel syndrome. J Gastroenterol **49**: 1193-1205, 2014.
16. Esposito I, de Leone A, Di Gregorio G, et al. Breath test for differential diagnosis between small intestinal bacterial overgrowth and irritable bowel disease: an observation on non-absorbable antibiotics. World J Gastroenterol **13**: 6016-6021, 2007.
17. Majewski M, Reddymasu SC, Sostarich S, Foran P, McCallum RW. Efficacy of rifaximin, a nonabsorbed oral antibiotic, in the treatment of small intestinal bacterial overgrowth. Am J Med Sci **333**: 266-270, 2007.
18. Peralta S, Cottone C, Doveri T, Almasio PL, Craxi A. Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with Rifaximin. World J Gastroenterol **15**: 2628-2631, 2009.
19. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol **33**: 550-558, 2015.
20. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology **60**: 715-735, 2014.
21. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the north american consensus. Am J Gastroenterol **112**: 775-784, 2017.
22. Kimer N, Krag A, Møller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Aliment Pharmacol Ther **40**: 123-132, 2014.
23. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med **362**: 1071-1081, 2010.
24. Zhang Y, Feng Y, Cao B, Tian Q. Effects of SIBO and rifaximin therapy on MHE caused by hepatic cirrhosis. Int J Clin Exp Med **8**: 2954-2957, 2015.
25. Kawaguchi T, Konishi M, Kato A, et al. Updating the neuropsychological test system in Japan for the elderly and in a modern touch screen tablet society by resetting the cut-off values. Hepatol Res **47**: 1335-1339, 2017.
26. de Lacy Costello BP, Ledochowski M, Ratcliffe NM. The importance of methane breath testing: a review. J Breath Res **7**: 024001, 2013.
27. Quigley EM, Abu-Shanab A. Small intestinal bacterial overgrowth. Infect Dis Clin North Am **24**: 943-959, 2010.
28. Bauer TM, Schwacha H, Steinbrückner B, et al. Diagnosis of small intestinal bacterial overgrowth in patients with cirrhosis of the liver: poor performance of the glucose breath hydrogen test. J Hepatol **33**: 382-386, 2000.
29. Sundin OH, Mendoza-Ladd A, Morales E, et al. Does a glucose-based hydrogen and methane breath test detect bacterial overgrowth in the jejunum? Neurogastroenterol Motil **30**: e13350, 2018.