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Evaluation of ammonia metabolism in the skeletal muscles of patients with cirrhosis using N-13 ammonia PET

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Objective: Skeletal muscle is said to compensate for the decreased ammonia metabolism in patients with cirrhosis. Branched-chain amino acids (BCAA) are being used as a treatment for hyperammonemia, and are believed to decrease blood ammonia by consumption of BCAA in skeletal muscles. We examined ammonia metabolism of the skeletal muscles in patients with liver cirrhosis after administration of BCAA using ^{13}N-ammonia positron emission tomography (PET). ***Methods:*** The subjects were patients with compensated or decompensated liver cirrhosis. PET studies were performed before and 2 hours after injection of BCAA. Serial dynamic PET scans (2 min × 10 frames) were started simultaneously with ^{13}N-ammonia injection. The standardized uptake value (SUV) of both thighs was calculated. ***Results:*** In the patient with compensated liver cirrhosis, there was little difference in the rate of increase in SUV before to after administration of BCAA. However, in the patient with decompensated liver cirrhosis, the rate of increase in SUV after administration was higher than that before administration of BCAA. ***Conclusion:*** Ammonia metabolism in the muscle of patients with liver cirrhosis could be examined noninvasively under physiological conditions using ^{13}N-ammonia PET. The muscles were found to metabolize ammonia partially, and the role of this contribution to metabolism of ammonia in patients with decompensated liver cirrhosis is particularly important.

Key words: liver cirrhosis, N-13 ammonia, positron emission tomography, BCAA

INTRODUCTION

AMMONIA is considered the major pathogenetic factor of hepatic encephalopathy.[1] It has been reported in animal experiments that skeletal muscles compensate for the decreased ammonia metabolism in cirrhotic liver.[2,3] Recently, infusion of branched-chain amino acids (BCAA), isoleucine, leucine and valine, has been used as a treatment for hyperammonemia, and is believed to decrease blood ammonia level by consumption of BCAA in skeletal muscles.[4]

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Positron emission tomography (PET) with ^{13}N-ammonia has been widely used for the evaluation of myocardial perfusion.[5,6] We examined ammonia metabolism in the skeletal muscles in patients with liver cirrhosis before and after administration of BCAA using ^{13}N-ammonia PET.

MATERIALS AND METHODS

Patients

The subjects were patients with cirrhosis with underlying hepatitis C virus infection. Case 1 was a 68-year-old man diagnosed with compensated liver cirrhosis. Case 2 was a 69-year-old woman diagnosed with decompensated liver cirrhosis. Decompensated liver cirrhosis was identified by the presence of jaundice, ascites and/or encephalopathy. The laboratory data and characteristics of both patients are shown in Table 1. This study conformed to the ethical guidelines of the Declaration of Helsinki and was

Table 1 Characteristics of two patients with cirrhosis

	Case 1	Case 2	Normal range
Sex	Male	Female	
Age (yo)	68	69	
NCT (sec)	36	82	0–50
Ascites	Absent	Present	
Encephalopathy	Absent	Present	
Varices	Absent	Present	
Serum albumin (g/d*l*)	4.2	3.1	3.5–5.0
Serum cholinesterase (IU/*l*)	396	228	350–750
Total bilirubin (mg/d*l*)	0.6	2.1	0.2–1.0
Prothrombin time (%)	150	63	80–120
Platelet counts (/mm^3)	14.6	6.2	18.0–34.0
Blood ammonia (μg/d*l*)	52	120	0–70
BTR	6.60	2.09	4.4–10.0

NCT, number connection test; BTR, branched-chain amino acid/tyrosine molar ratio

Table 2 SUV of both thighs in two patients

	Before injection of BCAA			After injection of BCAA		
	SUV 1	SUV 10	SUV dif	SUV 1	SUV 10	SUV dif
Case 1	0.28	0.60	0.32	0.26	0.78	0.52
Case 2	0.43	1.10	0.67	0.49	1.54	1.05

SUV 1, mean SUVs of both thighs at frame 1; SUV 10, mean SUVs of both thighs at frame 10; SUV dif, difference between SUV 10 and SUV 1

approved by the Ethics Committee of Osaka City University Medical School. Informed consent was obtained from both patients.

PET study

^{13}N-ammonia was produced with an NKK-Oxford superconducting cyclotron and an NKK synthesis system (AMANO1, NKK Co., Muroran, Japan). PET images were obtained by a PET scanner (HEADTOME IV SET-1400W-10, Shimadzu Co., Kyoto, Japan), which had 4 detector rings providing 7 contiguous slices at 13-mm intervals with an intrinsic resolution of 4.5 mm full width at half maximum (FWHM). Attenuation correction of the reconstructed images was accomplished by acquiring a patient-specific transmission study using a ^{68}Ge ring source. PET studies were performed before and 2 hours after drip injection of 500 m*l* of BCAA (Morihepamin, AJINOMOTO Pharmaceutical Co., Ltd., Tokyo, Japan). Serial dynamic PET scans (2 min × 10 frames) were started simultaneously with a 185 MBq ^{13}N-ammonia injection. For quantitative evaluation, ROIs were placed over both thighs (Fig. 1). The average activity within each ROI was subsequently corrected for radioactive decay, and standardized uptake values (SUV) were calculated by dividing the tissue activity by the injected dose of radioactivity per unit body weight.

RESULTS

The changes in mean SUVs in both thighs of the two patients are shown in Figure 2. After intravenous administration of ^{13}N-ammonia, SUV in the skeletal muscles increased gradually in both patients. The difference of SUV from the last frame to the first frame before administration of BCAA was higher in case 2 than in case 1 (0.67 and 0.32, respectively; Table 2). In case 1, there was little difference in the rate of increase in difference of SUV before to after administration of BCAA (0.20). However, the rate of increase in difference of SUV before to after administration in case 2 was high (0.38). In case 1, the blood ammonia level decreased from 54 to 48 μg/d*l* following BCAA therapy. In case 2, it decreased from 112 to 86 μg/d*l* after the same therapy.

DISCUSSION

Hepatic encephalopathy is one of the causes of death of patients with liver cirrhosis, and treatment of this encephalopathy is thus important for patients with liver cirrhosis. Ammonia plays a major role in the pathogenesis of hepatic encephalopathy.[1] Ammonia is mainly generated *in vivo* by deamination of amino acids in proteins ingested as food, but some is produced by intestinal bacteria.[7] The generated ammonia reaches the liver through the portal vein, is converted to urea by means of the urea cycle and excreted from the kidney. In patients with decreased hepatic functional reserve or those with portosystemic shunt, ammonia level in the blood rises. The excessive ammonia in such cases is mainly metabolized in skeletal muscles. However, skeletal muscles have no urea cycle, and therefore metabolize ammonia by producing glutamine from glutamate.[3] BCAA is required for this reaction.[4]

The radioactivity counts in the first part of the time-activity curve seem to reflect blood flow in the muscles. However, since isotopes in the blood decrease rapidly thereafter, the subsequent rise in counts seem to reflect increased uptake of ^{13}N-ammonia by muscles. Moreover, the greater radioactivity increase observed following BCAA therapy, as compared to the pre-therapy increase rate, seems to indicate increased uptake by muscles, since BCAA is not known to increase blood flow in the muscles. The increase in radioactivity in both patients by administration of BCAA indicates that BCAA assisted ammonia metabolism in the muscle in patients with liver cirrhosis. Furthermore, the SUV elevation after treatment with BCAA in decompensated liver cirrhosis was more distinct than that in compensated liver cirrhosis. This shows that excess ammonia which cannot be metabolized in the liver is released into the blood and metabolized in the muscles in cases of decompensated liver cirrhosis. Although animal experiments regarding this issue have been reported,[2] examination in humans has not been reported.

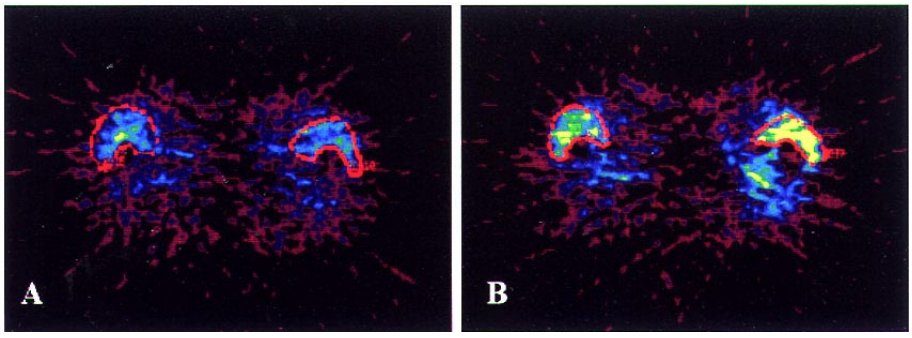

Fig. 1 Imaging of ^{13}N-ammonia PET. For quantitative evaluation, ROIs were placed over thighs. A: First frame in case 2 before injection of BCAA. B: last frame in case 2 before injection of BCAA.

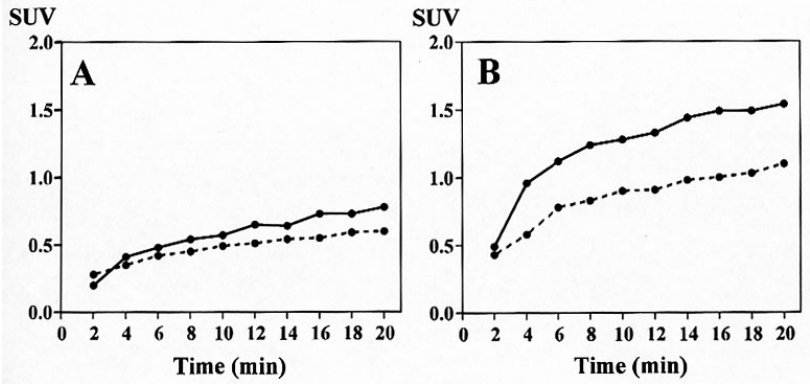

Fig. 2 A: Time activity curves of SUV in case 1. B: Time activity curves of SUV in case 2. Dotted line, before administration of BCAA; Continuous line, after administration of BCAA.

Using ammonia PET, detailed investigation of the role of ammonia metabolism in the muscle in patients with hepatic encephalopathy, which reflects the prognosis of patients with cirrhosis, will be possible in the future.

CONCLUSION

Ammonia metabolism in the muscle of patients with liver cirrhosis could be examined noninvasively under physiological conditions using ^{13}N-ammonia PET. The muscles were found to metabolize ammonia partially, and the role of this contribution to metabolism of ammonia in patients with decompensated liver cirrhosis is particularly important.

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