Normal Protein Diet and L-Ornithine-L-Aspartate for Hepatic Encephalopathy

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ABSTRACT

Excessive protein intake can cause hepatic encephalopathy (HE). Restricting protein in HE is becoming a controversy, because it can worsen malnutrition. This article reports the case of an under nourishment HE which is treated with L-ornithine-L-aspartate (LOLA) and given appropriate diet according to the nutrition status.

A 62-year-old man came with chief complaint of having reduced consciousness since 6 hours before admission. He had been diagnosed as liver cirrhosis for 6 years. Several days prior to admission he took high protein diet. Physical examination revealed under nutrition and unconsciousness. Hepatic encephalopathy was confirmed with low critical flicker test (CFF), and high blood ammonia level. He was treated with adequate diet and LOLA to decrease blood ammonia and improve the CFF. During the treatment, consciousness improved to normal, CFF increased and ammonia level decreased.

In this case, the HE was treated with LOLA without protein restriction. The HE improvement, in this circumstance may be caused of LOLA treatment that helps decrease the plasma ammonia level.

Adequate diet, 35-40 kcal/kgBW/d and protein intake 1.5 g/kgBW/d, has been administered safely to this patient with stage II hepatic encephalopathy. LOLA seemed to be effectively reduced ammonia level and improved the encephalopathy.

Key words: *liver cirrhosis, hepatic encephalopathy, L-ornithine L-aspartate, critical flicker test, blood ammonia level.*

INTRODUCTION

Liver cirrhosis is the end of various type of liver disease. It can evoke various complications such as reduced of liver synthetic function (coagulopathy), reduced liver capability for detoxification (hepatic encephalopathy), and portal hypertension with all its complications.[1,2] Hepatic encephalopathy (HE) is one of liver cirrhosis complications that brings high morbidity and mortality effects. The incidence rate of HE in liver cirrhosis are various from 30-45%[3] and also 50-70%,[4] where most of it is considered as minimal HE.

Increases of ammonia levels in the blood, among others, is the effect of over intake protein and gastrointestinal bleeding, until now has been considered to have the major role in HE pathogenesis.[4,5] Due to that, the management of HE especially tends to reduce the amount of ammonia in the blood, besides to overcome the initiating factor. The efforts to reduce the amount of ammonia in the blood are done by giving lactulose, antibiotics for intestine sterilization, and constrict the protein intake. Constricting protein intake in HE nowadays is becoming a controversy, because it can worsen malnutrition.[6] Many researcher reported that malnutrition can increase mortality rate in liver cirrhosis.[6-8] Contrariwise, nutrition improvement can increase muscle mass, which is needed for ammonia detoxification.[7] For the nutrition improvement a diet of 25-35 kcal/Kg per day and protein 1-1.5g/Kg/day is suggested.[7,9]

LOLA nowadays is started to be used to overcome HE since it is proven can reduce ammonia level in the blood,[8] LOLA stimulates the urea cycle and glutamine synthesis, which is the important mechanism in ammonia detoxification.[10,11] With the intake of LOLA

it is intended to reduce the ammonia level in the blood, so that it is unnecessary to constrict protein intake in liver cirrhosis patients with malnutrition.

This article reports the case of hepatic encephalopathy which is treated with LOLA and given 35 kcal/kg/day diet and 1.5g/kg/day protein.

CASE ILLUSTRATION

Patient is a 62 year old man who was brought in the emergency ward with chief complaint of reduced consciousness which manifested as having had difficulty in speaking since 6 hours prior to hospital admission. From his history of illness, patient had been experiencing fatigue and loss of balance since 3 days prior to admission. Furthermore, patient constantly felt drowsy; therefore, his sleeping hours increased in both duration and frequency and family members often unable to comprehend what the patient said. Six hours prior to admission, he was unable to recognize the people around him, further deterioration of speech skills; therefore, family members decided to bring him to the emergency ward of Tebet Hospital Jakarta.

Patient was diagnosed with liver cirrhosis due to hepatitis B infection 6 years prior to admission. His symptoms were swollen abdomen and feet which resolved every time he received medications from the doctor. He always performed his check-up routinely every month up to this incident; furthermore, he also paid high attention to his daily diet which was specifically recommended by a nutritionist. However, since several days prior to admission, patient's serum albumin level had been low, therefore his wife decided to add more fish into his daily diet.

During physical examination in the emergency ward, the patient was deemed with moderately ill condition with disorientation. His body height was 168 cm; his weight was 62 kg and *mid arm muscle circumference* (MAMC) 228 mm. He had normal blood pressure, no signs of fever, however abnormalities were found in his eyes which had anemic conjunctiva and icteric sclera. Other abnormalities seen were *spider nevi* on the chest and *palmar erythem* on his extremities. In addition, collateral veins were discovered on his abdomen with enlarged spleen up to shuffner II, with no signs of ascites or extremity edema, and a flapping tremor was also noticeable.

Laboratory results on admission showed a condition of pancytopenia (Hb 11,7 g/dl, leukocyte 3270/uL, platelets 65.600/uL, LED 50 mm/jam. Electrolyte balance and prothrombine time were under normal limits. Albumin was 2,4 g/dl, total bilirubin 1,98 mg/dl, SGOT 75 iu/L, SGPT 32 iu/L. Urinalysis tests showed no abnormalities and were under normal limits.

Current working diagnosis on arrival is hepatic encephalopathy due to increased protein intake on cirrhotic patient due to chronic hepatitis B infection. Pancytopenia was suspected due to hypersplenism with liver cirrhosis. USG of the abdomen is planned to confirm the cirrhosis, blood ammonia level as well as critical flicker test (CFF) to confirm hepatic encephalopathy. The patient was given a diet of 2100 calories daily with 90 grams protein along with substituted branch chained amino acids (BCAA), L-ornithine L-aspartate (Hepamerz) I.V. 20 grams of (4 ampoules) / day in 250 ml of infuse line for 5 days and later replaced with oral route 3 x 6 grams for 2 weeks in order to reduce the ammonia levels in the blood. Lactulose of PO 4 x 15 ml was administered to facilitate transit to reduce further breakdown of ammonia.

During the follow up, we acquired the abdominal USG results which confirmed the diagnosis of liver cirrhosis and splenomegaly with minimal ascites. Ammonia level showed 189 mmol/L (normal < 54mmol/L), CFF 33,8 Hz (normal ≥39 Hz). These results further strengthened the diagnosis of hepatic encephalopathy on liver cirrhosis. After 2 days of treatment, patient's condition improved with increased consciousness level up to fully alert, and no flapping tremor was noticeable. Repeated measurement of blood ammonia levels shows an improvement (reduction up to 155 mmol/L) and furthermore, CFF had increased up to 38.8 Hz.

DISCUSSION

This is a case of liver cirrhosis with the complication of encephalopathy due to excessive protein intake. Excessive protein intake is one of several initiating factors of HE that cause increased ammonia production.[1] Forty per cent of ammonia is generated by the intestine from nitrogenate substances, caused by the action of bacterial urease and amino acid oxidases, and the other 60% is derived from the metabolism of glutamine and the transamination of other amino acids.[15] In normal subjects, intestinal ammonia, produced from nitrogen products, is taken up by the liver and metabolized to urea. In liver cirrhosis, damaged livers do not accomplish this step adequately, and splanchnic blood flow do not allow to penetrate into the parenchyma; then, portosystemic shunts are created and ammonia and other metabolites are sent to the systemic circulation and finally reach the brain. Ammonia inhibits excitatory post-synaptic potentials,

thereby, producing a general depression of the CNS function.[15]

Encephalopathy diagnosis was proven with the increased of ammonia level, which supported the theory that acknowledge that ammonia hold an important role in the HE mechanism. Laboratory results of 2.4 g/dl albumin level, 1.98 mg/dl total bilirubin level, normal prothrombine time, minimal ascites (under control) and minimal encephalopathy shows that liver function level of the patient is classified as Child Pugh B so the possibility of HE due to endogen factor is not likely.

Flicker test nowadays is considered as a sensitive test, simple, and reliable to diagnose HE in liver cirrhosis.[12,13] The CFF of 33.8 ± 0.58 Hz in this patient showed the existence of HE caused by increased ammonia level due to increased protein intake priory.

The patient has 22,1 kg/m2 BMI (Body Mass Index) that shows normal nutritious, but apparently MAMC shows that actually the patient has started to undergo minor malnutrition. It was known that the weight of liver cirrhosis patients was more affected by ascites and edema, therefore calculation and measurement using MAMC suggested to evaluate nutrition status.[14]

According to European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines 1997, protein intake should decrease to 0.5–1.5 g/kg body weight/day if stage I or II encephalopathy is present and to 0.5 g/kg body weight/day if stage III or IV encephalopathy is present.[8,9] However, in this stage II HE patient, protein intake did not decrease to 0.5-1.5 g/kgBW. The patient was given normal diet for liver cirrhosis without encephalopathy, 35-40 kcal/kgBW/d and protein intake 1.5 g/kgBW/d, to avoid worsening of malnutrition.[8,9]

The improvement of HE in this patient, although receiving normal protein diet, is supported by studies of Cordoba[16] and Gheorghe.[17] Cordoba compared the effects of low and normal protein diet in HE, and found that normal protein diet can be administered safely to cirrhotic patients with episodic hepatic encephalopathy.[16] Gheorghe noted that dietary protein restriction is not required for the improvement of HE.[17] These findings support that low protein diet is not required and is better avoided in treating HE.

The patient was given protein diet with branch chain amino acid (BCAA) substitute, in order to improve the nutritional status. The usefulness of branched-chain amino acid (BCAA) supplementation in patients with cirrhosis has long been debated. It was proposed that depletion of BCAAs, as seen in many patients with advanced liver disease, might promote the development of hepatic encephalopathy by enhancing the passage of aromatic amino acids across the blood–brain barrier, resulting in the synthesis of false neurotransmitters. For this reason, it was hypothesized that BCAA supplementation might improve hepatic encephalopathy. However, some controlled trials showed no benefit of BCAAs in hepatic encephalopathy with BCAA treatment. Contrariwise, there is evidence of the beneficial effects of BCAAs in the treatment of malnutrition in patients with advanced cirrhosis.[8]

To overcome the increasing ammonia level, the patient was given LOLA 20 g intravenous (4 ampoules dissolved in 250 cc carrier solution over 4 hours) for 5 days followed by LOLA granules 6 g three times daily for 2 weeks. LOLA acts to stimulate the urea cycle and glutamine synthesis which are important mechanisms in ammonia detoxification, and by that it is considered an ammonia lowering treatment.[7,11] Many clinical trials found that LOLA improved HE better than placebo.[11,18-20] Furthermore, giving LOLA in this patient reduced the risk of increasing ammonia level due to non restriction of protein diet. It appears that the normal protein diet given to this patient did not worsen EH, in this circumstance may be caused by LOLA treatment that helps decreasing the plasma ammonia level.

CONCLUSION

Adequate diet, 35-40 kcal/kgBW/d and protein intake 1.5 g/kgBW/d, has been administered safely to this patient with stage II hepatic encephalopathy. LOLA seemed to be effectively reduce ammonia level and improve the encephalopathy.

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