

Do Hepatic Encephalopathy Patients Really Need a Low Protein in Their Diet?

Sudomo U, Lelosutan ARS*, Ruswhandi*, Akbar Nurul***

* Division of Gastroentero-hepatology, Department of Internal Medicine
Central Army Hospital Gatot Soebroto, Jakarta

** Division of Hepatology, Department of Internal Medicine, Faculty of Medicine
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

ABSTRACT

Hepatic encephalopathy (HE) is an extra hepatic complication of liver cirrhosis. The clinical manifestation of HE is a reflection of a low-grade cerebral edema due to astrocyte swelling as a consequence of hyperammonia. HE mostly is induced by precipitating factors. Correcting these identifiable precipitating factors can alleviate this complication. In the past, liver cirrhosis patients were recommended to lower their protein intake. It was assumed that by limiting protein intake, the ammonia production would lower, which can lead to HE recovery. This approach, on the other hand, had worsened the nutritional status that already present in most patients with HE. There are some ways to overcome these problems without restricting protein intake including balance diet, using Branch Chain Amino Acids (BCAA), and frequent small portion diet.

Keywords: *hepatic encephalopathy, astrocytes swelling, ammonia, liver cirrhosis, BCAA*

INTRODUCTION

Hepatic Encephalopathy (HE), an extra-hepatic complication of impaired liver function that may be present in 50-70% of all liver cirrhosis patients, is a neuron-psychiatric syndrome, which can develop in acute or chronic liver disease.^{1,2} It remains a major cause of morbidity and mortality in chronic liver disease.

The clinical manifestations of HE range from subtle abnormalities detectable only by psychometric testing to deep coma. Formerly, those manifestations were thought to be due to the false neuron transmitters. However, recent evidences reveal that those are as reflection of a low grade cerebral edema due to astrocyte swelling which is aggravated by precipitating factors.^{3,4} In this context, astrocyte plays an important role as major site of ammonia detoxification in HE.

The aim of treating these patients is to treat the identifiable precipitating factors, which can lead to

recovery from an episode of HE. Additional measures are applied to enhance recovery e.g. limiting the generation or absorption of ammonia from the gut.

PATOPHYSIOLOGY

Depending on the appearance and the speed of the development of the precipitating factors, the magnitude of liver damage and the portal-systemic, HE can be divided in two forms of manifestations: porto- systemic encephalopathy and the HE with acute liver failure.

The acute form of HE can rapidly progress to full-blown syndrome, which does not respond to treatment and has unfavorable prognosis. The chronic form of HE is more common than the acute form, occurring in up to 50-80% of liver cirrhosis patients.⁵ The symptoms of mental states gradation are shown in table 1.

In the past studies of HE focused primarily on the impaired neurotransmission observed in hyperammonia. Evidence-based medicine showed that disturbances of neurotransmission in HE seem to be due to astrocytes swelling leading to astrocyte dysfunction.

Under physiological metabolic conditions, ammonia is present in the blood (normal peripheral blood

Correspondence: Untung Sudomo
Division of Gastroentero-hepatology
Department of Internal Medicine
Central Army Hospital Gatot Soebroto
Jl. Dr. Abdul Rachman Saleh No. 22-24 Jakarta, Indonesia
E-mail: tupdalam@yahoo.com

Table 1. Mental state gradation of HE severity (West- Haven criteria) ⁶

Hepatic Encephalopathy Grade	Clinical Symptoms
0	No overt symptoms; no pathological psychometric
Minimal (sub clinical, latent)	No overt symptoms; pathological psychometric
I	Disturbed sleep-wake rhythm, restless, irritability, euphoria, anxiety, aimless, shortened attention span, trivial lack of awareness, impaired performance of addition
II	Lethargy or apathy, overt personality changes, lassitude, minimal disorientation for time and space, memory weakness, yawning, impaired performance of subtraction. Inappropriate behavior
III	Somnolence to semi-stupor, confusion, disturbed articulation responsive to verbal stimuli, gross disorientation

NH₃ = 30 mmol/liter), crosses the blood-brain barrier, and enters the astrocytes, where it binds glutamate synthetase to glutamate, giving rise to glutamine. To maintain glutamine level within physiological level, the excess is removed from the astrocytes through specific transport system, since the blood-brain barrier is impermeable to amino acids.

Hyper-ammonia in HE, whether it comes from intestinal over production due to dietary protein overload, obstipation, GI tract bleeding, tissue bleeding, azotemia or extra intestinal caused by catabolism (in septic condition, infections, surgical intervention or fever), could lead to deleterious effect. Excessive amount of ammonia reaches the astrocytes, which in turn increasing the level of glutamine inside the astrocytes, reaching beyond physiological high level limit in these cells. Glutamine; just like ammonia, is osmotically active. It causes more water enter the astrocytes, and makes these cells swell.⁵

In acute HE, astrocytes swelling occurs rapidly and develops into brain edema. Since it develops rapidly in progressing liver failure with increasing blood ammonia level, the brain cells do not have sufficient time or capacity to overcome this osmolarity disturbance.⁵

In chronic HE, on the other hand, brain edema is rare. Since this form of HE develops insidiously, and blood ammonia level increase slowly, the astrocytes are initially able to compensate, at least in part for osmotic effect of ammonia. Nevertheless, some astrocytes swelling also develop.

Ammonia in HE also affects permeability of the astrocytes membrane that is not more permeable generally; rather, it seems that only affects specific transport mechanism.⁵ It is supported by the fact that steroids do not have any effect on cerebral edema in HE-in contrast to stroke, where such edema regresses rapidly by steroid administration.

Despite hyper ammonia is the cause in inducing astrocytes swelling that lead to HE, there is no correlation between blood ammonia concentration with the degree of HE. Suspected HE must then be confirmed by different diagnosis, and a search

Table 2. Principles of the treatment of HE.⁶

Eliminating of precipitating factors
<ul style="list-style-type: none"> - Stop GI bleeding, evacuation of blood from the GI tract, avoidance of too many blood transfusions - Avoidance of azotemia - Arterial hypotension and hypoxemia - Reduction of diuretic therapy to an acceptable minimum - Stop dehydration, correction of water and electrolyte imbalance, avoidance of hypokalemia or excessive ascites paracentesis - Strict avoidance of benzodiazepines, sedative or other psychoactive drugs

undertaken for possible liver disease. Because majority HE is induced by precipitating factors, treatment is aimed to to these abnormalities.

There are three sources where ammonia comes from: first, it comes from the large bowel. colonic flora convert urea as protein metabolite into ammonia which in normally converted back to urea by the liver. The second source (less important) of ammonia comes from converted glutamine by renal tubular and the last ammonia comes from the catabolism of protein, urea and DNA. Hyperammonia can be originated from the increase of intestinal (due to dietary protein overload, obstipation, GI bleeding, azotemia) and/or elevated extra intestinal (catabolism due to septic, infections, surgical intervention, fever.⁷ Ammonia is metabolized in the liver and outside the liver (brain, muscle and other tissue). In cirrhotic liver, this capacity is reduced leading to increased burden of brain (astrocytes) and other tissue to eliminate/metabolize this substance.

The brain of cirrhotic patients with HE consistently show a depletion of myo-inositol accompanied by an increase in the ratio glutamine/glutamate signal, which indicates astrocytes swelling as an early pathogenetic event in HE.¹ It was suggested that the increase in brain water not merely results from ammonia induced astroglial glutamine accumulation, but also induced by other HE-relevant factors.

Diet of liver cirrhosis patients

Energy and protein balance can be obtained by providing 30-40 kcal/kgBW/day and the amount of

protein intake which will assure nitrogen balance in most patients is around 1.2-1.3 g/kg BW/day.⁸ Cirrhosis patients utilize dietary protein very efficiently. With increasing dietary protein, the increase in nitrogen retention was 85% of the protein intake. This utilization is similar to that of malnourished individuals without any organ disease.⁸

In the past patients with liver disease were instructed to limit their protein intake in their diet because high protein ingestion was assumed to increase ammonia production which induce HE. This approach of cause aggravated the nutritional depletion that typically already present in patients with chronic liver disease whose prevalence as high as 65-90%, depending on etiology of disease (alcoholic-non alcoholic) and the severity of liver failure.^{9,10} Inadequate protein intake can cause a negative nitrogen balance and tissue catabolism that may aggravate HE by increasing the plasma and brain contents of aromatic amino acids (phenylalanine, tyrosine, tryptophane). These patients should therefore, consume normal amount of protein in their diet, and only small group of them with end stage liver disease cannot tolerate normal diet. BCAA (valine, leucine, and isoleucine) may be beneficial for some patients who are judge to be protein intolerant.⁸ BCAA stimulates insulin production and increase uptake sugar and amino acid. It is also differently metabolized in the muscle not like other amino acids, which are broken down in the liver. All of the three BCAA have to be available at the same time to ensure maximum utilization and should be taken on empty stomach because they actively compete with other amino acids for uptake and utilization.¹¹

Boon L et al, found in rats that ingestion of liberal amounts of dietary protein, promote urea cycle enzymes and enable adequate protein metabolism.⁹ This phenomenon, even in small sample size, was also demonstrated in patients with HE.¹² They proved that there was no different of plasma ammonia, bilirubin, prothrombine activity, albumin level between group patients who received low protein (30 cal/kgBW/day; protein < 1.2 g/kg BW/day) with those who had normal protein diet (30 cal/kgBW/day, protein 1.2 gram/kgBW/day). However, there was exacerbated protein breakdown in the low protein group without differences in protein synthesis. As the protein intake in both group were equalized, there were no differences in either protein synthesis or breakdown.

ESPEN 1997,¹³ recommended protein intake for HE patients 0.5 g/kgBW/day in short time, and then increase it to 1.0-1.5 g/kg/day with non protein energy 25-35 cal/kgBW/day. The ESPEN 2006,¹⁴ recommended energy intake of 35-40 cal/kgBW/day and protein 1.2-1.5 g/kg BW/day for liver cirrhosis patients and BCAA enriched formulae should be used

in patients with hepatic encephalopathy occurred during enteral nutrition.

Condition in which “amino acid toxicity” occurs is in GI bleeding in liver cirrhosis patients. Self-digestion of blood will induce encephalopathy due to lack of essential amino acid isoleucine in hemoglobin which make it as a protein of biologically low value. The lack of protein synthesis leads to elevate plasma amino acids levels including leucine and valin e without isoleucine. The high level of valin and leucine stimulate BCAA dehydrogenase which in turn lead to degradation of all BCAA including isoleucine; that will aggravates amino acids imbalance further.¹⁵

To overcome the reducing capacity of the cirrhotic liver to metabolize ammonia, it is thought to lower ammonia level by (1) decreasing ammoniogenic substrate and (2) lowering ammonia production.

Decreasing ammoniogenic substrate

In the past, by reducing of total protein intake only for short time was presumed to be useful to improve HE grade.¹³ Recently, this approach has been challenged. The other method is by utilizing less comagenic types of protein. Blood protein and meat protein are more ammoniogenic and presumably more comagenic than vegetable protein.

Vegetable protein is better tolerated by patients susceptible to HE This beneficial effect may be due to its higher content of fiber in vegetable protein than in animal protein with an equal amount of nitrogen. The fiber increases the transit time of food through the intestine and lower the pH of colonic lumen as a result of its fermentation by colonic bacteria.^{7,16}

Lowering ammonia production

It is already known that ammonia is produced mainly in the gut and extra intestinal from protein. Thus, the quantity and the quality of protein as part of bolus meal must be taken into consideration e.g. its composition, digestibility, absorption of the amino acids.¹⁷

Amino acid composition suitability of protein in the meal is those, which are very gradually delivered into the portal and subsequently into the systemic circulation. This will give more time to the already decreasing ability of cirrhotic liver cell to metabolize ammonia produced. This composition depends on (1)nutritional co-factors that promote protein synthesis, decelerate the post prandrial appearance of amino acids in the portal vein, diminish urea synthesis, and improve nitrogen balance. Those factors include adding carbohydrates to protein and adding essential amino acids to the low value protein, (2) the quality of protein itself. After digestion, re-sorption, and re-synthesis process, protein is slowly degraded and released as amino acids into portal vein. In turn, this leads to better

utilization of these amino acids in the liver or elsewhere in the body and to low levels of urea production. In addition, slow stomach emptying or slow digestion of protein adds beneficial effect. Casein is a slow protein partly because of its coagulation in the stomach and subsequent slow passage and digestion and (3) the labile protein pool: proteins that temporarily accumulate after meal in the gut include in this setting as enzymes synthesized in the process of digestion and secreted into the gut, mucus, and enterocytes in the gut lumen.

Application of those mentioned above in daily life, it is recommended for cirrhotic patients (even healthy individuals) to eat balance food with high quality protein, combined with other nutrients including macronutrient such as carbohydrates in frequent small portions. When most of the protein is taken up during one meal, the gut is unable to assimilate a large proportion of it because the capacity of the labile protein pool is exceeded.¹⁸ This will exceed the capacity of the cirrhotic liver to metabolize as well.¹⁷

CONCLUSION

Hepatic Encephalopathy (HE) is an extra hepatic complication of impaired liver function, manifested from mild abnormality psychometric test to deep coma, caused by astrocyte swelling. The swelling of astrocytes is not merely caused by hyper-ammonia, but many factors involved.

In addition to correct precipitating factors that induce HE, giving appropriate diet will mostly improve the HE. It has been proven that providing diet to HE patients equal with those normal people with calorie intake 30-40/kgBW/day and protein intake 1.2-1.3 g/kgBW/day, showed more beneficial effects than restricted protein diet as majority current diet protocols.

It is recommended to eat balance food with high quality protein combined with other macronutrients in frequent small portions. Protein with less ammoniogenic/comagenic effect e.g. vegetable protein is more preferable. For those who show any protein intolerant effects during treatment such as worsen the degree of HE, it is recommended to change to BCAA enriched diet.

REFERENCES

- Häussinger D, Launberger J, vom Dahl S, et al. Proton magnetic resonance spectroscopy on human brain myo-inositol in hypo-osmolarity and hepatic encephalopathy. *Gastroenterology* 1994;107:1475-80.
- Häussinger D, Kircheis G, Fischer R, et al. Hepatic encephalopathy in chronic liver disease a clinical manifestation of astrocyte swelling and low grade cerebral edema. *J Hepatol* 2000;32:1035-38.
- Häussinger D, Schleiss F, Kircheis G, et al. Pathogenesis of hepatic encephalopathy. *J Gastroenterol Hepatol* 2003;17: S256-S259.
- Srivastava N, Singh N, Joshi YK. Nutrition in the hepatic encephalopathy. *Trop Gastroenterol* 2003;24:59-62.
- Anonymous. Organic and systemic detoxification of ammonia in hepatic and systemic ammonia detoxification in the treatment of hepatic encephalopathy. 10th International Symposium on Hepatic Encephalopathy. Suppl for Internists. Istanbul Turkey May 1999.
- Kircheis G, Timmermann L, Schnitzler A, Häussinger D. New diagnostic and therapeutic options in hepatic encephalopathy. Post graduate course and current reviews in hepatology. APASL 2004 (India).
- Kircheis G, Häussinger D. Management of hepatic encephalopathy. *J Gastroenterol Hepatol* 2002;17:S260-S267.
- Kondrup J, Müller MJ. Energy and protein requirements of patients with chronic liver disease. *J Hepatol* 1997;27:239-247.
- Boon L, Geerts WJ, Jonker A, et al. High protein diet induces pericentral glutamate dehydrogenase and ornithine aminotransferase to provide sufficient glutamate for pericentral detoxification of ammonia in rat liver lobules. *Histochem Cell Biol* 1999;111:445-52.
- Neuschwander, Tetri BA, Caldwell SH. Non alcoholic steatohepatitis: summary of an AASLD single topic conference. *Hepatology* 2003;37:1202-19.
- Abou-Assi S. Symposium hepatic encephalopathy. Metabolic consequence of cirrhosis often is reversible. *Postgrad Med* 2001;109(2):52-70.
- Córdoba J, López-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of randomized study. *J Hepatol* 2004;41:38-43.
- Plauth M, Merli M, Kondrup J, et al. ESPEN guidelines for nutrition in liver disease and transplantation. *Clin Nutr* 1997;16:43-55.
- Plauth M, Cabre E, Riggio O, et al. ESPEN guidelines on enteral nutrition: Liver disease. *Clin Nutr* 2006;25:285-94.
- Olde Damink SW, Jalan R, Deutz NE, et al. The kidney plays a mayor role in the hyper ammonia seen after simulated or actual gastro-intestinal bleeding in patients with cirrhosis. *Hepatology* 2003;37:1277-85.
- Riordan SM, William R. Treatment of hepatic encephalopathy. *NEJ Med* 1997;337(7):473-9.
- Soeters PB, van de Poll MCG, van Gemert WG, et al. Amino acid adequacy in pathophysiological states. *J Nutr* 2004;134:1575S-82S.
- van der Schoor SR, van Goudover JB, Stoll B, et al. The pattern of intestinal substrate oxidation is altered by protein restriction in pigs. *Gastroenterology* 2001;121: 1167-75.