Commentary

What Improves Minimal Hepatic Encephalopathy: Probiotic Yogurt, Protein Restriction or Nonabsorbable Disaccharides?

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Hepatic encephalopathy (HE) is a neuropsychiatric disorder associated with liver failure or porto-systemic venous shunting and characterized by personality changes, intellectual impairment, and an altered level of consciousness.

In 2002, a working committee task force on HE standardized the definition and the classification of HE. According to the characteristics of neurological manifestations, HE is classified as episodic (previously acute), persistent (previously chronic), or minimal (previously subclinical).[1] Minimal hepatic encephalopathy (MHE) is the mildest form of the spectrum of HE. Patients with MHE have no clear clinical symptoms but only some subtle cognitive deficits and psychomotor abnormalities that mainly affect immediate memory, attention, visual-spatial abilities, and fine motor skills.[2] MHE is an important disorder that impairs the patients' daily functioning, including driving skills and health-related quality of life and may progress to overt HE.[3]

Ammonia is an important factor in the pathogenesis of MHE. Serum concentrations of ammonia are elevated in cirrhosis; however, it is known that the correlation between the plasma ammonia levels and the degree of HE is poor. MHE is estimated to have a prevalence ranging from 22% to 80%.[4,5] The prevalence of MHE in extra-hepatic portal vein obstruction (EHPVO) patients is 35.3%.[6,7]

Sharma *et al*. studied the incidence of overt HE development in EHPVO patients with MHE, and found that 75% of EHPVO patients with MHE continued to have MHE, while new-onset MHE developed in 5% over a 1-year period. In this study, patients with EHPVO and MHE did not progress to overt encephalopathy within the studied time frame.[6]

The improvement of cognitive function remains the main goal of the MHE treatment. Most of the available MHE treatment strategies concentrate on reducing serum ammonia levels by decreasing ammonia production and increasing its elimination. Measures have utilized several modalities, which showed improvement in psychometric performance and quality of life. These modalities include lactulose, minimizing dietary protein, branched-chain amino acids,[8] L-ornithine L-aspartate (LOLA)[9] probiotics and synbiotics,[10,11] and antibiotics.

In the past, low-protein diet was recommended for patients with HE as it was thought to decrease the production of intestinal ammonia and thus the severity of HE. In a randomized controlled trial, patients received either low-protein diet or normal protein diet together with the standard treatment regimen. The outcome of HE was not significantly different between the two groups.[12] In addition, high fiber diet may be helpful in decreasing the colonic transit time and absorption of ammonia.[13] It is not clear however if this is relevant to MHE related to EHPVO, as all reported data were studied in patients with HE due to cirrhosis.

Lactulose is a nonabsorbable disaccharide, and its mechanism of action is not precisely known. A recent meta-analysis of lactulose in MHE showed that lactulose prevented the progression to overt HE, reduced blood ammonia levels, and improved health-related quality of life. However, no significant difference was observed in the mortality of patients with MHE, and lactulose significantly increased the incidence of diarrhea.[14]

Probiotic yogurt is basically a yogurt with live and active cultures. Lactic acid bacteria and Bifidobacteria are the most common types of microbes used as probiotics, although certain yeasts and bacilli may also be used.[15] Probiotics are useful in the treatment of HE by reducing ammonia in the portal blood by decreasing bacterial urease activity in the intestinal lumen, by decreasing ammonia absorption by decreasing intestinal pH, and by improving nutritional status of gut epithelium resulting in decreasing intestinal permeability, and decreasing inflammation and oxidative stress in the hepatocyte leading to increased hepatic clearance of ammonia.[3]

Bajaj and colleagues[11] investigated the use of probiotic yogurt for the treatment of MHE in patients with nonalcoholic cirrhosis. Yogurt was chosen because it is a palatable food item, is widely available and does not require prescription, all of which favor long-term adherence.

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Complete reversal of MHE was achieved in only those patients who consumed yoghurt (71%, $P=0.003$) and was associated with improvement in psychometric test results. Probiotic yogurt may represent a safe, effective, and long-term therapy for MHE. In an open label randomized controlled trial of lactulose and probiotics in the treatment of MHE, 55% of the patients with cirrhosis had MHE. Lactulose or probiotics or combinations of both were equally effective in the treatment of MHE.[16]

In this issue of the Journal, in the first study of its kind, Sharma and colleagues[17] present their experience in the treatment of MHE in patients with EHPVO with lactulose. In 70 patients with EHPVO, 30 were diagnosed with MHE based on extensive pretreatment testing that includes the positivity of two psychometric tests, measurement of critical flicker frequency threshold and arterial ammonia. The same testing was repeated after 3 months of lactulose therapy to assess for complete reversal of the initial findings. The investigators clearly followed their cohort for sufficient time after therapy to observe for treatment effect. Moreover, they evaluated for adherence to therapy and encouraged follow-up visits by contacting patients who did not show up for evaluation. Their results reveal that the incidence of MHE in patients with EHPVO was 43% and lactulose improved MHE in 53% of these patients after 3 months of treatment. Other strength points in the study includes; utilization of objective parameters in assessment of response and the use of specific endpoint that was the complete reversal of MHE at 3 months.

The study nonetheless has several shortcomings. A major drawback is the lack of a control arm to account for the possible improvement in MHE to other confounding factors. This is relevant since spontaneous improvements in MHE are not uncommon as previously reported by the authors.[6] Additionally, since they were comparing outcome difference they should have calculated the relative risk (RR) and subsequently the absolute risk reduction (ARR) between pre and post lactulose treatment. They should have also reported the confidence interval (CI), as the magnitude of the relative risk and the size of confidence interval will be more informative and better counted than just *P*-value only.

The question that remains unanswered is whether lactulose alone would be sufficient for treating MHE? Is it better than the healthier and safer alternative in probiotic yogurt? Gaseous distension, abdominal cramps, dehydration, and poor compliance are strong limiting factors against the routine use of lactulose. Probiotics may be better option since they are safe, effective, and widely available, and can be used as a long-term therapy in the treatment of MHE. Nevertheless, Sharma *et al*.[17] address an issue where scant knowledge exists. These findings should be further studied and validated in larger, multicenter, and randomized-controlled trials.

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REFERENCES

1. 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 2002;35:716-21.
2. Randolph C, Hilsabeck R, Kato A, Kharbanda P, Li YY, Mapelli D, *et al*. Neuropsychological assessment of hepatic encephalopathy: ISHEN practice guidelines. Liver Int 2009;29:629-35.
3. Dhiman RK, Chawla YK. Minimal hepatic encephalopathy. Indian J Gastroenterol 2009;28:5-16.
4. Sharma P, Sharma BC. Predictors of minimal hepatic encephalopathy in patients with cirrhosis. Saudi J Gastroenterol 2010;16:181-7.
5. Bajaj JS. Minimal hepatic encephalopathy matters in daily life. World J Gastroenterol 2008;14:3609-15.
6. Sharma P, Sharma BC, Puri V, Sarin SK. Natural history of minimal hepatic encephalopathy in patients with extrahepatic portal vein obstruction. Am J Gastroenterol 2009;104:885-90.
7. Sharma P, Sharma BC, Puri V, Sarin SK. Minimal hepatic encephalopathy in patients with extrahepatic portal vein obstruction. Am J Gastroenterol 2008;103:1406-12.
8. Holecek M. Three targets of branched-chain amino acid supplementation in the treatment of liver disease. Nutrition 2010;26:482-90.
9. Abdo-Francis J, Perez-Hernandez J, Hinojosa-Ruiz A, Hernandez-Vasquez J. Use of L-ornitin L-aspartate (LOLA) reduces time of hospital stay in patients with hepatic encephalopathy. Rev Gastroenterol Mex 2010;75:135-41.
10. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004;39:1441-9.
11. Bajaj JS, Saeian K, Christensen KM, Hafeezullah M, Varma RR, Franco J, *et al*. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. Am J Gastroenterol 2008;103:1707-15.
12. Cordoba J, Lopez-Hellin J, Planas M, Sabín P, Sanpedro F, Castro F, *et al*. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41:38-43.
13. Bianchi GP, Marchesini G, Fabbri A, Rondelli A, Bugianesi E, Zoli M, *et al*. Vegetable versus animal protein diet in cirrhotic patients with chronic encephalopathy. A randomized cross-over comparison. J Intern Med 1993;233:385-92.
14. Luo M, Li L, Lu CZ, Cao WK. Clinical efficacy and safety of lactulose for minimal hepatic encephalopathy: a meta-analysis. Eur J Gastroenterol Hepatol 2011;23:1250-7.
15. Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria (October 2001). Available from: http://www.who.int/entity/foodsafety/publications/fs_management/en/probiotics.pdf. [Last accessed on 2012 Mar 25].
16. Sharma P, Sharma BC, Puri V, Sarin SK. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol 2008;20:506-11.
17. Sharma P, Sharma BC. Lactulose for minimal hepatic encephalopathy in patients with extrahepatic portal vein obstruction. Saudi J Gastroenterol 2012;18:168-72.