CORRESPONDENCE

The Diagnosis and Treatment of Minimal Hepatic Encephalopathy

by Dr. med. Tianzuo Zhan, Prof. Dr. med. Dr. h.c. med. Wolfgang Stremmel
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Restricting Protein Intake not Beneficial

Zhan and Stremmel correctly draw attention to minimal hepatic encephalopathy (MHE), a frequently unrecognized complication of cirrhosis. They highlight the dilemma that restriction of dietary protein intake further reduces muscle mass in patients who are already severely malnourished. In the section on nutritional therapy, however, the authors fail to make clear statements. The European Society for Clinical Nutrition and Metabolism (*Europäische Gesellschaft für Stoffwechselforschung und klinische Ernährung*, ESPEN) guideline recommending a protein rich diet is based on evidence from randomized controlled trials (1) and should not be dismissed. Even in patients with recurrent encephalopathy, protein restriction—as previously recommended—is not beneficial (2). The often reiterated recommendation of protein restriction is based on a collection of cases reported by Sherlock and colleagues in 1954. Here they described a selected subgroup of five patients with cirrhosis and encephalopathy, four of whom suffered from portal vein thrombosis and two of whom were treated with ammonium chloride as a diuretic. „Meat intoxication“ as a precipitating factor of hepatic encephalopathy is a rare event nowadays and listing excessive protein intake as item number 2 in the box showing precipitating factors is not appropriate. Infections are far more important in that respect and should be systematically and rapidly sought for and treated; indeed, infections should be at the top of the list.

Furthermore, an effect of lactulose on ammonia generation from the glutamine metabolism of the small intestinal mucosa can only be exerted by small bowel evacuation but not by a specific effect on glutamine uptake (3). The work of Egberts and Schomerus on the effect of branched-chain amino acids on driving capacity seems to have escaped the authors' attention when compiling the list of randomized controlled trials.

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REFERENCES

1. Kearns P, Young H, Garcia G, et al.: Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology* 1992; 102: 200–5.
2. Córdoba J, López-Hellín J, Planas M, et al.: Normal protein for episodic hepatic encephalopathy: results of a randomized trial. *J Hepatol* 2004; 41: 38–43.
3. Plauth M, Raible A, Graser TA, et al.: Lactulose or paromomycin do not affect ammonia generation in the isolated perfused rat small intestine. *Z Gastroenterol* 1994; 32: 141–5.

4. Zhan T, Stremmel W: The diagnosis and treatment of minimal hepatic encephalopathy. *Dtsch Arztebl Int* 2012; 109(10): 180–7.

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Conflict of interest statement

The authors has received honoraria for acting as an expert adviser from Baxter Advisory Board, lecture honoraria from Falk Foundation, Nestlé, Baxter, Roche, and Ardeypharm, and honoraria for conducting several clinical phase II/III trials.

Will Health Insurers Cover the Costs?

The authors of the review article recommended treatment with lactulose and rifaximin 550 mg twice daily for three to six months. This raises the question of how this recommendation—administration of a nonabsorbable antibiotic—is to be implemented into practice. Theoretically, the daily treatment costs for rifaximin 1100 mg amount to a minimum of 15 euros, which translates into about 2700 euros for six months. Rifaximin is currently not licensed for this indication, and doctors can therefore not prescribe it. Will the health insurers cover these costs?

It was not mentioned whether rifaximin was tested against another substance (antibiotic) as placebo. For clinically practicing physicians, it is of importance that any therapeutic recommendation is easy in implementation and suitable for 2012. The authors should mention which established antibiotic treatment is recommended alternatively.

Additionally there might be readers who would like to know whether the authors themselves prescribe rifaximin for their patients. DOI: 10.3238/arztebl.2012.0502b

REFERENCES

1. Zhan T, Stremmel W: The diagnosis and treatment of minimal hepatic encephalopathy. *Dtsch Arztebl Int* 2012; 109(10): 180–7.

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The author declares that no conflict of interest exists.

In Reply:

We thank our correspondents for their comments on our article. Our response is shown below:

- The recommendation for a restriction of protein intake is indeed the subject of diverging opinion. Phongsamran et al (1) have also regarded that protein restriction is not substantiated by any evidence. We concede that the listing of excessive protein as item 2 in the box of precipitating factors equates to over-rating the effects of protein.

- Upon reading the article written by Plauth et al (2), one is indeed led to conclude that “the effect of lactulose on ammonia generation from glutamine through the mucosa of the small intestine has been shown only for the evacuation of the intestinal lumen and not for a specific effect on glutamine uptake.”
- The mention of Egberts and Schomerus and their study findings on improved driving performance as a result of branched-chain amino acids is fully justified.
- The therapeutic option of rifaximin 550 mg twice daily was derived from published studies and its use as approved therapy in the US.
- Our article did not focus on cost speculation. The theoretical calculation of treatment costs is specious because until rifaximin is, as expected, licensed for the treatment of hepatic encephalopathy in the German market, the price for a required dosage has yet to be decided.
- In addition to lactulose, Phongsamran et al in their article suggested other options for antibiotic treatment of hepatic encephalopathy, such as vancomycin, metronidazole, and neomycin. Because

of poor clinical effectiveness, high costs (vancomycin), and potential adverse effects (neomycin), their use as prophylaxis is at the very least controversial.

- In certain circumstances, we consider the use of rifaximin to treat our patients.

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REFERENCES

1. Phongsamran PV, Kim JW, Cupo Abbott J, Rosenblatt A: Pharmacotherapy for hepatic encephalopathy. *Drugs* 2010; 70: 1131–48.
2. Plauth M, Raible A, Graser TA, et al.: Lactulose or paromomycin do not affect ammonia generation in the isolated perfused rat small intestine. *Z Gastroenterol* 1994; 32: 141–5.
3. Zhan T, Stremmel W: The diagnosis and treatment of minimal hepatic encephalopathy. *Dtsch Arztebl Int* 2012; 109(10): 180–7.

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The authors holds shares in Gilead and has received travel expenses and lecture honoraria from Falk-Symposium.