Management of Covert Hepatic Encephalopathy

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Hepatic encephalopathy is a reversible progressive neuropsychiatric disorder that encompasses a wide clinical spectrum. Covert hepatic encephalopathy is defined as patients with minimal hepatic encephalopathy and Grade I encephalopathy by West-Haven Criteria. Terminology such as "sub-clinical", "latent", and "minimal" appear to trivialize the disease and have been replaced by the term covert. The lack of clinical signs means that covert hepatic encephalopathy is rarely recognized or treated outside of clinical trials with options for therapy based on patients with episodic hepatic encephalopathy. This review discusses the current available options for therapy in covert hepatic encephalopathy and focuses on non-absorbable disaccharides (lactulose or lactitol), antibiotics (rifaximin), probiotics/synbiotics and L-ornithine-L-aspartate. (J Clin Exp Hepatol 2015;5:S75–S81)

Hepatic encephalopathy (HE) is a reversible progressive neuropsychiatric disorder occurring in patients with significant liver disease. It encompasses a clinical spectrum of symptoms involving psychomotor, intellectual, cognitive, and motor function.[1] Minimal hepatic encephalopathy (MHE) presents with a normal neurologic examination and no obvious clinical signs, but subtle changes in attention, psychomotor speed, and executive decision making.[2] Prior terminology included "sub-clinical", "latent", and "minimal" appear to trivialize the condition. There is abundant evidence in the literature that MHE has a profound impact on quality of life, daily functioning, driving ability,[3–10] and nearly half of all patients with MHE may be unfit to maintain employment.[9] Based on the current ISHEN guidelines,[11] patients with MHE and Grade I encephalopathy by West-Haven Criteria were re-classified as having covert hepatic encephalopathy (CHE). Since the prevalence of MHE in patients with cirrhosis varies between 30 and 84%,[12–15] therapeutic strategies to prevent overt hepatic encephalopathy (OHE) are of major importance.

Treatment options for CHE are derived from prior experience in patients with episodic HE. Given the lack of clinical signs, CHE is rarely recognized or treated outside of clinical trials. Many therapies have been tested based on theories of the pathogenesis of HE. These include N-methyl-D-aspartate antagonists, N-acetylcysteine, anti-inflammatories (cyclo-oxygenase inhibitors), flumazenil, and bromocriptine. However, all have been abandoned because of evidence of lack of efficacy or adverse safety profile. Circulating levels of ammonia and other gut derived toxins are central to the pathogenesis of HE and remain the target of therapy in CHE. The gut microbiota plays an integral role in the production of ammonia and other toxins resulting in oxidative stress/inflammation.[16–19] It would only seem natural that treatment modalities in CHE would focus on the modulation of the gut flora. Therapeutic strategies for CHE must be extrapolated from MHE trials as CHE is a relatively recent term and no studies on therapy are available at this time. This review discusses the currently available treatment options for CHE.

NON-ABSORBABLE DISSACHARIDES

Lactulose

Lactulose or lactitol are synthetic non-absorbable disaccharides, that are extensively used in the management of OHE. Lactulose is fermented in the colon into acetic and lactic acid resulting in acidification of intestinal contents and conversion of ammonia (NH_3) to ammonium (NH_{4+}). Unlike ammonia, ammonium is not systemically absorbed and is excreted in stool. Lactulose also has a cathartic effect increasing nitrogen excretion by four

Keywords: hepatic encephalopathy, lactulose, rifaximin, probiotics
Received: 7.1.2014; *Accepted:* 19.2.2014; *Available online:* 1.4.2014
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Abbreviations: HRQoL: health-related quality of life; CFF: critical flicker frequency; NCT-A: number connection tests A; NCT-B: number connection tests B; DST: digit symbol test; OCTT: orocecal transit time; FOS: fructo-oligosaccharides; BAEP: brain auditory evoked potential; BDT: block design test; LCT: line tracing test; RCT: race track test; ICT: inhibitory control test; SDMT: Symbol digit modalities test; TMT: Trail making test; SPT: standard psychometric test; NPE: neuropsychological exam; PCT: Picture completion test; FCT-A: Figure connection test-A; PSE: psychometric testing; SDT: serial-dotting test; APT: abnormal psychometric testing
http://dx.doi.org/10.1016/j.jceh.2014.02.007

Treatment

fold.[20–22] Recommendations supporting lactulose as the preferred therapeutic option in OHE are based on 2001 guidelines which were developed prior to a number of significant trials in alternative therapies such as rifaximin or probiotics.[20] In a recent survey, 78% of gastroenterologists have extended the use of lactulose to first line therapy in the treatment of MHE.[23]

In a randomized open label trial, lactulose therapy 30–60 mL/day was compared to no treatment in patients with cirrhosis and MHE.[24] Compared to the untreated group, there was a significant decrease in the number of abnormal psychometric tests in the group treated with lactulose ($P < 0.0001$). Treatment also demonstrated a significant improvement in the health-related quality of life (HRQoL) vs. those who did not receive lactulose [6.81 vs 0.17 (95% CI, 5.24–8.37) and (95% CI, −0.29 to 0.63), respectively; $P < 0.001$].[24] Sharma et al further reported the benefit of lactulose therapy for the primary prevention of OHE in patients with cirrhosis. A total of 120 cirrhotic patients with no prior episode of OHE were randomized to receive lactulose (55 patients, 32/55 with MHE) or no treatment (50 patients, 36/50 with MHE), with progression to OHE assessed over 12 months. MHE was diagnosed by psychometric and critical flicker frequency testing, while the West-Haven Criteria was used to grade OHE. Lactulose protected against the progression to OHE (11% of patient receiving lactulose and 28% in the control group developed OHE, $P = 0.02$) and 66% of the patients diagnosed with MHE responded to treatment. Therefore, lactulose was deemed to be effective in the primary prevention of overt hepatic encephalopathy.[25] Congruent with prior results, several other studies have reported an improvement in neuropsychometric tests with various doses and durations of lactulose and lactitol treatment[25–30] (Table 1).

In a meta-analysis of five studies (total, $N = 170$ patients), lactulose treatment demonstrated a benefit for MHE (RR 0.34, 95% CI, 0.24–0.47; $P < 0.0001$).[31] Luo et al further corroborated these findings in a meta-analysis of 9 randomized studies (total, $N = 434$ patients). Analysis revealed a significant reduction in the mean number of abnormal neuropsychological tests, blood ammonia levels, progression to OHE (RR: 0.17, 95% CI, 0.06–0.52, $P = 0.002$), and improved HRQoL.[32] The results support the safety and efficacy of lactulose treatment for MHE.

Diarrhea, abdominal pain/cramping, nausea, and flatulence are among the most common dose related adverse effects limiting adherence.[25,28,33,34] In a trial of 128 cirrhotic patients, Kalaitzakis et al reported that daily lactulose had a negative impact on HRQoL.[35] The laxative effect and titration to 2–3 soft bowel movements per day make adherence to lactulose classically low.[12] Paradoxically, overuse of lactulose can result in severe dehydration and hyponatremia leading to worsening of HE. Interestingly, a lower serum sodium (less than 132.5 mmol/L) and a higher ammonia level (greater than 93.5 mmol/L) were two parameters that correlated with lactulose failure.[36] Lastly, as stated earlier, all of the trials presented above were completed in MHE; therefore caution should be used when translating this data to CHE.

Antibiotics

The goal of antibiotic therapy remains the suppression of urease producing intestinal organisms, thereby reducing serum levels of ammonia and other gut derived toxins (eg, mercaptans, phenols, oxindole, and short chain fatty acids).[22,37,38] Oral antibiotics (eg, neomycin, metronidazole, vancomycin, and paromycin) have demonstrated varying degrees of success in the treatment of OHE. However, systemic adverse events including nephrotoxicity, ototoxicity, peripheral neuropathy, antibiotic resistance, and the risk of Clostridium difficile colitis and vancomycin resistant enterocolitis (VRE) has limited their role in the treatment of MHE.

Rifaximin

Rifaximin is an oral non-systemic broad spectrum antibiotic that is structurally similar to Rifampin. By binding to bacterial DNA-dependent RNA polymerase, rifaximin inhibits bacterial RNA/protein synthesis. Structurally, the benzimidazole ring limits systemic absorption to 0.4%,[39] with the primary mode of excretion via feces and low levels of drug excreted in urine or bile.[40,41] Concentrated in the gut, rifaximin is presumed to modulate intestinal bacteria, thereby reducing intestinal ammonia and toxin formation.[42] In a recent open labeled trial, Bajaj et al performed a systems biologic analysis of the microbiome and evaluated cognitive changes after treatment with rifaximin (550 mg bid) in 20 cirrhotic patients diagnosed with MHE. Therapy was associated with improved cognitive function and reduced endotoxemia. Moreover, treatment with rifaximin resulted in a modest change in stool microbiota characterized by a reduction in *Veillonellaceae* and an increase in *Eubacteriaceae*. *Veillonellaceae* are gram negative cocci that are more abundant in the stool of patients with cirrhosis compared to healthy individuals.[16]

The initial studies for rifaximin demonstrated its efficacy in the management of OHE. Compared to lactulose, rifaximin is more effective in the treatment of OHE.[43] In a randomized double-blind placebo controlled trial (total, $N = 299$ patients) over a 6-month-period, rifaximin (550 mg twice daily) reduced the risk of an episode of OHE and the time to first hospitalization, with no serious adverse events.[44] Moreover, Neff et al recently showed that rifaximin use for greater than 6 months proved to be effective in the management of HE, especially in patients with MELD ≤ 20.[45]

Because of its documented safety and efficacy in patients with OHE, the investigation of rifaximin in the

