30 *Management of Hepatic Encephalopathy: Seen and Unseen*

Radha K Dhiman, Kuldip K Solanki

Abstract: Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction and/or porto-systemic shunting of the intestinal blood after exclusion of other known brain abnormalities. HE is a form of gliopathy caused due to swelling of Alzheimer type II astrocytes. Ammonia is primarily responsible for encephalopathy and has been substantiated by recent studies. West Haven criteria are the most acceptable grading system for HE. Non-absorbable disaccharides and antibiotics are mainstay of therapy.

Minimal hepatic encephalopathy(MHE) seriously impairs daily activities and health related quality of life (HRQOL) in patients with cirrhosis. It predicts development to overt encephalopathy and is associated with poor prognosis. Diagnosis of MHE requires a high index of suspicion. Combination of at least two psychometric (trailmaking tests, block design or digit symbol test) and one neurophysiological test (P300 BAEP or electroencephlography with mean dominant frequency) are optimal in detecting MHE.

Treatment with lactulose is of benefit as it improves both cognitive functions and HRQOL. Treatment with synbiotics or fermentable fiber is an alternative to lactulose for management of MHE in patients with cirrhosis. Cirrhotic patients may be routinely screened for the presence and treatment of MHE.

INTRODUCTION

Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction and/or porto-systemic shunting of the intestinal blood after exclusion of other known brain abnormalities.

Nomenclature and Grading of Hepatic Encephalopathy

Working Party at the 11th World Congress of Gastroenterology, Vienna, under the Organization Mondiale de Gastroentrologie proposed multiaxial definition of HE that defines both the type of hepatic abnormality and the duration/characteristics of neurological manifestations in chronic liver disease (Table 30.1). HE has been considered a continuous dimension that could be measured with one index to summarize several neurological domains, such as, cognition, emotion, behavior, or biologic rhythms. Minimal hepatic encephalopathy (MHE) would represent a portion of this dimension, would be the mildest form of HE, and would be diagnosed on the basis of a cut-off score (Fig. 30.1).[1]

The West Haven criteria for semiquantative grading of mental state still remains the most acceptable (Table 30.2).[1]

Patients with HE also have innumerable changes in motor function like rigidity, disorders of speech, resting and movement induced tremor, asterixis, delayed diadochokinetic movements, hyper or hyporeflexia, choreoathetoid movements, Babinsky's sign and transient focal symptoms.[2,3] These patients with HE also demonstrate a wide spectrum of abnormalities like disturbed neurophysiological functions,[4] impaired psychomotor performance[5], altered cerebral neurochemical/ neurotransmitter homeostasis,[6] reductions in global and regional cerebral blood flow and metabolism.[7]

Diagnosis of Hepatic Encephalopathy

HE is a diagnosis of exclusion and it is important to exclude CNS disorders like intracranial space occupying lesions, vascular events and infections diseases in patients with liver disease.
Asterixis, a cardinal sign is HE may also be present is uremia, CO_2 narcosis, phenytoin intoxication and hypomagnesemia. The choice of tests to exclude other causes of altered sensorium needs to be individualized but may include: brain imaging, such as CT scan or MRI; lumbar puncture in subjects with fever, leukocytosis and meningeal signs, and automated analysis of EEG.

Precipitating Factors for Hepatic Encephalopathy

Evaluation should include work up to look for the precipitating factors and strict attention must be paid in treating following precipitating factors:

1. *Infection:* Spontaneous bacterial peritonitis, urinary or respiratory tract infections; appropriate cultures are required.
2. *Nitrogen overload:* Gastrointestinal bleed, uremia, constipation and or excessive consumption of proteins, etc; placement of nasogastric tube and stool analysis is required to exclude gastrointestinal bleed.
3. *Metabolic:* Hypokalemia, alkalosis, hyponatremia, renal failure, dehydration: prompt identification followed by correction of these metabolic factors are mandatory.
4. *Additional hepatic injury:* Portal vein thrombosis or superimposed hepatitis (viral, alcoholic or drug induced).
5. *Drugs:* Opiates, benzodiazepines, sedatives, diuretics: urinary screening for narcotics or benzodiazepines may be required at times.

Pathogenesis of Hepatic Encephalopathy

HE is a form of gliopathy[8] caused due to swelling of Alzheimer type II astrocytes, the only cerebral cell capable of metabolizing ammonia. Ammonia and other intestinal neurotoxins, manganese and the benzodiazepine-GABA system are the main substances implicated in the development of HE. Neurotransmission changes induced by these compounds play a major role in the development of the neurologic disturbances presented in these patients.

Ammonia remains the first key gut-derived neurotoxin implicated in the pathogenesis of HE; the highest concentrations are found in the portal vein. Ammonia, derived from colonic bacteria as well as from the deamination of glutamine in the small bowel, is absorbed by passive diffusion and undergoes a high first-pass extraction by the liver. In liver failure, hepatic urea synthesis declines and this, along with portal-systemic shunting, leads to increased arterial blood ammonia concentrations. Ammonia is primarily responsible for encephalopathy that has been substantiated by recent studies.[9,10] A study has shown that arterial ammonia levels > 200 μg/dl in patients with stages III-IV encephalopathy were an accurate predictor of herniation in patients with acute liver failure.[11]

The blood-brain barrier permeability to ammonia is increased in patients with HE. Ammonia is detoxified in astrocytes by glutamine synthetase leading to formation of glutamine, the accumulation of which is the major cause of astrocyte swelling.[12]

Ammonia also effects the neurons by inducing neurosteroid production leading to a positive modulatory effect on the γ-aminobutyric acid A (GABA-A) receptors leading to upregulation of peripheral benzodiazepine receptors thus causing a functional imbalance between the excitatory and inhibitory receptor systems. The upregulation of GABA-A receptors in HE is a form of denervation supersensitivity and is associated with decreased GABA at neuronal level rather than an increased GABA levels in blood and brain. Indeed, animal studies have shown that mild encephalopathy is characterized by a 45-50% increase in the number of GABA receptors without change in the affinity constants.[13,14] These findings have recently been confirmed in humans where increased central type benzodiazepine receptors and decreased cortical GABA levels were demonstrated in patients with recurrent HE.[15] Thus, these changes explain the supersensitivity to benzodiazepines in patients with acute and chronic liver disease.

Hence ammonia induces HE by multiple mechanisms and is the main pathogenetic factor.

Natural benzodiazepines (NBZDs) such as diazepam and nordiazepam are naturally present in several plants, vegetables, and animal species and in humans.[17] Microorganisms in gut flora like *Acinetobacter lwoffi* can also produce NBZDs. NBZDs are found in trace amount in normal subjects but may increase several fold in patients with cirrhosis.[16] A significant but weak correlation between NBZDs and the degree of HE has been demonstrated by Basile and co-workers.[18] A recent study showed a 40% reduction in NBZDs levels after reduction in bacterial flora with riflaximin.[18] Thus NBZD might be contributing to the pathogenesis of HE.

Treatment of Hepatic Encephalopathy

Based on pathogenetic mechanisms several therapeutic modalities have been used to treat hepatic encephalopathy (Table 30.3). However, their efficacy has been seldom assessed by well-designed randomized clinical trials.

Table 30.3: Treatment of hepatic encephalopathy

Principle	*Agents*
Decrease nitrogen load from the gut	• Dietary protein restriction • Catharsis • Antibiotics • Synbiotic
Improve extra-intestinal elimination of NH_3	• L-ornithine L-asparatate • Oral zinc • Sodium benzoate
To counteract abnormalities of central neuro-transmission	• Flumazenil • Branched chain amino acids • Bromocriptine

Dietary Proteins

Curtailment of dietary proteins for a few days is commonly practiced in HE. Recent research, however, has shown that protein requirements are increased in these patients.[19] A restrictive protein diet worsens the nutritional status of the patients, does not improve the outcome of HE and can actually lead to an increase in ammonia due to reduction in the muscular removal of this substance. In this connection, a recent study has shown that a normoproteic diet can be safely administered to patients with acute HE.[20] High protein diets are well tolerated and their use, particularly in patients who are malnourished, is associated with sustained improvement in mental state.[21,22] European Society for parenteral and enteral nutrition has recommended that

traditional protein restriction should be abandoned in patients with HE particularly as other effective treatments are available. Daily protein intake of 1-1.5 gm/kg/day has been recommended.[23] A positive nitrogen balance prevents gluconeogenesis and thus increases the capacity of muscles to detoxify ammonia.

Catharsis

Nonabsorbable disaccharides - lactutose and lactilol have been the first line therapy for HE. These are not metabolized in small bowel. On reaching into large bowel, they are metabolized by colonic bacteria into acetic acid and lactic acid. Acidification of colon induces catharsis and favours the passage of NH_3 into the colonic lumen. Therapy should be aimed to attain 2 to 3 semisolid stools. The mean daily doses ranged from 30-84 gm in ten trials with 280 patients.[24] Lactulose and lactilol can also be administered as enemas. A solution of 1000 ml (300 ml lactulose + 700 ml water) is placed into the colon, with patient in reverse Trendelenburg for one hour to ensure deeper entry into colon. Enema therapy is mainly beneficial in hastening the recovery in deeper states of encephalopathy. Potential adverse effects include protracted diarrhea, hypernatremia and hyperosmolarity.

Non-absorbable disaccharides seem to have been introduced into clinical practice without appropriate documentation. Though they have long been considered as first line therapy, in a recent systematic review, Als-Nielsen and colleagues[24] concluded that there is insufficient evidence to support or refute use of non-absorbable diasaccharides for HE. However, inconclusive results could be related to presence of confounding factors, such as, presence of precipitatory event(s), degree of hepatic failure and the extent of porto-systemic shunting in these studies. There is a need of further well-designed randomized controlled trials to document their effectiveness.

Other agents, which have been shown to be effective, are mannitol and colon cleansing agents used for endoscopic procedures. In one study irrigation with 5-liter isotonic solution of mannitol by a nasogastric tube was found to be effective in preventing post-gastrointestinal bleed HE.[25]

Antibiotics

Different antibiotics have been tested, both in open and controlled studies (Table 30.4).[26]

Antibiotic therapy was the first treatment proposed for HE on the basis of uncontrolled clinical trials.[27] Different antibiotics have been tested for their efficacy in HE (Table 30.4). A Cochrane review has shown that antibiotics are superior to nonabsorbable disaccharides in HE, however it was unclear whether this difference in treatment effect is clinically relevant.[24]

The prolonged use of antimicrobials as first line therapy is precluded by the possible occurrence of adverse events. Rifaximin, a poorly absorbed rifamycin derivative is an exception to this because it is remarkably safe in the long-term use.[26] It displays a wide spectrum of antibacterial activity against gram-negative and gram-positive bacteria, both aerobic and anaerobic, and a very low rate of systemic absorption. It has been assessed in about 16 clinical trials and has been found to improve clinical status, decrease blood ammonia levels and also reduce blood concentrations of endogenous benzodiazepines.[26] Rifaximin is currently not available in India.

PROBIOTICS

After antibiotics treatment, probiotics if continued have also been found to be beneficial in HE.[28]

L-ornithine L-aspartate (LOLA): In a study of 126 patients, intravenous infusion of L-ornithine L-aspartate (LOLA) 20 gm/day for 7 days showed better results than placebo.[29] In chronic encephalopathy, improvement with oral LOLA was more marked in stage II encephalopathy as compared to those with lower stages of HE. This combination provides substrate for the urea

cycle. It also leads to generation of glutamate through transamination, which in turn diverts NH_3 towards glutamine synthesis within muscle due to activation of muscle glutamine synthetase.

Oral zinc: Zinc is a cofactor in all enzymes of urea cycle. Zinc administration in animal models of cirrhosis has shown to improve urea synthesis.[30] Zinc acetate 220 mg bid is indicated in patients with associated malnutrition.

Sodium benzoate: It is converted in liver into benzoyl CoA which binds to glycine to form hippurate that is excreted in urine thus eliminating one nitrogen molecule for every benzoate molecule. In a study of 74 patients with acute encephalopathy randomized to lactulose verses 10 gm sodium benzoate, the improvement in HE was similar in both groups.[31] The effectiveness of benzoate in cirrhosis is less because of decreased liver function besides it also leads to worsening of ascites.

Flumazenil: Flumazenil acts by antagonizing endogenous benzodiazepines at the GABA-A receptor site. A meta-analysis has shown beneficial effects in 31% of patients by causing reduction in grade of HE within a short period of administration of flumazenil.[32]

Branched chain amino acids: Alterations in central neurotransmission occur possibly because of increased CNS entry of aromatic amino acids and reduction of branched chain amino acids pool. Branched chain amino acids probably have beneficial effects by enhancing peripheral metabolism of NH_3 in muscles.

Bromocriptine: Administration of bromocriptine, 30/mg/day showed improvement in extra-pyramidal symptoms seen in patients with cirrhosis of liver.

Minimal Hepatic Encephalopathy

MHE has generated a lot of interest in recent years. There is increasing evidence to show that MHE is an important disorder that could seriously impair daily living and health related quality of life (HRQOL) in patients with cirrhosis.[33-35] Treatment with lactulose is of benefit as it improves both cognitive functions and HRQOL.[33] Diagnosis of MHE requires a high index of suspicion.

Historical Aspects

In 1957, Passons-Smith, et al identified the presence of definite electroencephalographic (EEG) abnormalities in 43% of cirrhotic patients without overt HE. The authors did not realize the importance of their findings, which in effect defined the existence of a latent or preclinical stage of HE.

In 1970, Zeagen, et al, observed that 62% of a cohort of patients who had undergone porto-systemic shunt surgery showed impaired performance of the Trail-Making Tests A and B even though their mental function was apparently normal. In 1978, Rikkers, et al, evaluated a group of cirrhotic patients who had undergone porto-systemic shunt surgery but whose mental state was deemed to be unimpaired; they observed EEG abnormalities in 33% and impaired psychometric performance in 60%. The authors coined the term subclinical HE. Recently, use of the term subclinical HE has been criticized mainly because such a term might trivialize the condition because its presence has a detrimental effect on health related quality of life, may predict overt HE and may carry poor prognosis. Present consensus favors the term that was coined by Schomerus and Hamster. This term also signifies that MHE represents the mildest form of HE and represents one end of the continuous dimension (see Fig. 30.1).

Clinical Significance of MHE

Is MHE clinically significant? To address this question we need to discuss at least three issues, i.e., (i) Does MHE impairs daily functioning or HRQOL? (ii) What is its natural history? and (iii) Is it associated with poor prognosis? First, increasing evidence suggests that MHE is an important disorder that impairs patients daily functioning and HRQOL.[33-35] While the basic activities of daily life, such as shopping, dressing, personal hygiene, etc. are largely preserved; complex activities involving attention, information processing and psychomotor skills such as driving a car, planning a trip, etc. are mainly affected. Blue-collar workers suffering from cirrhosis with MHE are less likely to earn their wages than the white-collar workers.[35] In addition, psychometric studies have shown that patients with MHE may be unfit to drive a car.[36,38] In a landmark study, using a standardized 90-minute on-the-road driving test Wein and colleagues[38] reported that fitness to drive a car is impaired in cirrhotic patients with MHE; the ratings were worst in patients with MHE, while patients without MHE scored similar to controls. More importantly, the instructor had to intervene more frequently during the test to avoid accidents in patients with MHE (36%) than in those patients without MHE (6%) and controls (8%)[38]. The results of Wein's study suggest that MHE should be considered a medical condition that warrants treatment to improve psychomotor impairment. Second, natural history of MHE in cirrhotic patient is not widely studied. However, our and others observations indicate that MHE predicts the occurrence of overt HE.[39,40] Finally, the prognosis of MHE is also not clearly established. While Hartmann, et al, did not find any prognostic significance of MHE.[41] Amodio, et al,[42] found that computerized psychometric tests and quantifiable alterations in EEG predict poor prognosis. A pathological oral glutamine challenge response in patients with MHE also appears to be associated with the development of overt HE and poor survival.[43,44] MHE, therefore, is a clinically significant disorder that impairs HRQOL, predicts the development of overt encephalopathy, and is probably associated with poor prognosis.

Diagnostic tools for MHE

There are numerous modalities, which are used to diagnose MHE (Table 30.5).[46] However, traditionally the diagnosis has been limited to the presence of neurological impairment demonstrated by neuropsychological assessment or neurophysiological tests (Tables 30.6 and 30.7).[1,45,46]

Neuropsychological Assessment[45]

Neuropsychological (NP) (Table 30.7) methods have been the most trusted and widely used tests. A large number of psychometric tests have been used to detect cognitive abnormalities in patients with MHE. Unfortunately, the diagnostic approach to the assessment of MHE is not uniform; various combinations of psychometric tests with or without neurophysiological methods have been used to diagnose MHE by different groups of workers, making comparison between studies difficult and rendering the wide range of sensitivities and specificities quoted for the same tests in different studies hard to interpret.[45] Most of the studies have used trail making tests, various subtests of Wechsler Adult Intelligence Scale for verbal and nonverbal skills and other paper-pencil tests.

Promising results have been obtained using a short battery of five tests namely number connection tests A and B and the line tracing, a serial dotting and digit symbol tests. This battery is called as psychometric hepatic encephalopathy score (PHES) and examines motor speed and accuracy, visual perception, visuo-spatial orientation, visual construction, concentration, attention and to a lesser extent memory. Validation studies have been in Italian, German and Spanish populations. It is being validated by us in Indian population as well.

Table 30.7: Neurophysiological methods[45]

1.	**Electroencephalogram (EEG)**
	a. Standard

b. Mean dominant frequency

2. Evoked potentials
   a. Exogenous
      i. Brainstem auditory evoked potentials (BAEP)
      ii. Visual evoked potentials (VEP)
      iii. Somatosensory evoked potentials (SSEP)
   b. Event related potentials (P300)
      i. Visual paradigm
      ii. Auditory paradigm

3. Critical flicker frequency (CFF)

EEG

EEG can be assessed by means of simple visual reading and by quantitative methods such as spectral analysis. EEG is best assessed using spectral rather than visual analysis because its repeatability is greater. An objective classification of EEG alterations in HE, that was based on EEG parameters obtained by automatic quantitative spectral analysis, was proposed more recently by Van der Rijt, et al.[47] Such a technique increases the reliability of EEG assessment.[48] In the absence of other causes, the alterations observed in the EEG in cirrhotic patients are assumed to reflect the presence of MHE, since they roughly correlate with plasma ammonia concentrations and other indices of hepatic dysfunction, and predict the development of overt HE and liver related death, at least in patients with advanced liver disease.[49]

Event Related (Cognitive) Evoked Potentials

There are two kinds of evoked potentials, i.e. exogenous evoked potentials and endogenous event related potentials.

Event related endogenous potentials occur secondary to the stimulus processing response. They occur independent of the type of stimulus, and are a measure of the cognitive function responsible for processing the response to a stimulus. Therefore, these tests are sensitive in detecting subtle cognitive deficits, which are an integral part of the early stages of HE. Tests are carried out by giving either auditory or visual stimuli. Two types of stimuli are used, the "common or the frequent stimuli" interspersed randomly with the "target or rare stimuli" in ratio of about 80:20 respectively. The patient is asked to concentrate on the target stimuli only and register them by counting or indicating in some way. Potentials occurring in response to this process are recorded. The event related P300 wave is the most consistent wave and can be considered the electrophysiological counterpart of the psychometric tests as both involve active use of the cognitive faculties.

Saxena, et al[50] showed P300 was altered in 20-80% of cirrhotic patients with no clinical evidence of HE or with grade I changes. They also demonstrated, in a follow up study that changes in P300 latency predicted the occurrence of overt HE.

Critical Flicker Frequency

Other methods applied for detection of MHE include measuring of the CFF threshold at which light pulses are perceived as fused. Kircheis, et al[51] evaluated CFF in 92 patients with cirrhosis. The investigation is based on the suggested pathogenesis of HE, that low-grade astrocyte swelling is an early event and triggers HE by altering the glioneural communication. The authors based their study on the hypothesis that retinal gliopathy could serve as a marker of cerebral gliopathy in HE. They also performed psychometric tests in these patients. The authors defined a cut-off between normal and pathologic CFF of 39 Hz. Using this frequency as cut-off, CFF analysis detected MHE in about 30% of cirrhotic patients compared with about 50% with psychometric tests. Authors recommended CFF as a simple and reliable test for the diagnosis of

MHE after considering long time spent with psychometric tests. However, approximately 40% of the patients who were classified as MHE by the psychometric tests had normal CFF.[51] Therefore, CFF alone may not be adequate for the detection of MHE. Further studies are required in this field to confirm the efficacy of this test and its value in relation to psychometry and other neurophysiological tests.

Diagnosis of MHE

Various tools have been evaluated for the correct diagnosis of MHE and include the psychological tests, neurophysiological tests, regional cerebral blood flow changes and magnetic resonance spectroscopy. However, in the absence of a "*gold standard*" psychometric and neurophysiological methods have been the most trusted and widely used tests. Combination of at least two psychometric (trailmaking tests, block design or digit symbol test) and one neurophysiological test (P300 BAEP or electroencephlography with mean dominant frequency) appears to be optimal in detecting MHE.[1,45]

Treatment of Minimal Hepatic Encephalopathy

The pathogenesis of MHE is thought to be similar to that of overt HE and ammonia plays a key role.[51-53] Ammonia induced alterations in cerebral blood flow and glucose metabolism have shown that there is a significant decrease of glucose utilization of various cortical regions that correlate with the patients cognitive functions.[53]

Various treatment modalities have been tried to treat this condition, e.g. dietary protein manipulation,[54] branched-chain amino acids,[55] L–ornithine L–aspartate,[29] and lactulose.[33,56,57] Most of these therapies were aimed to reduce ammonia levels.

Non-absorbable Dissachharides

Lactulose is the most common agent used in the treatment of MHE. Treatment with lactulose is of benefit in majority of patients with MHE.[33,56,57] Watanabe, et al showed that MHE disappeared in 50% of patients treated with lactulose for 8 weeks but persisted in 85% of untreated patients.[57] We found marked improvement in psychometric tests with lactulose administration for 3 months; MHE disappeared in 8/10 patients on lactulose but persisted in all 8 untreated patients.[56] Lactulose lowers ammonia levels by alteration in gut flora resulting in decreased production and absorption of ammonia.

Dhiman and co-workers for the first time investigated the effect of treatment related improvement in cognitive functions on health related quality-of-life (HRQOL).[33] We measured psychometric performance by number and figure connection tests A and B, picture completion and block design tests, and HRQOL by Sickness Impact Profile (SIP) in 90 cirrhotic patients at inclusion into the study and 3 months thereafter. Sixty-one (67.7%) patients had MHE. They were randomly assigned in a 1:1 ratio to receive treatment (lactulose) for 3 months (n = 31) or no treatment (n = 30) in a non-blinded design. Mean number of abnormal NP tests decreased significantly in patients in treated group compared with patients in untreated group (MANOVA for time and treatment, P =.001). Intention to treat analysis showed that improvement following lactulose therapy was significant. While 20 out of 31 (64.5%) patients in treated group improved, 2 of 30 (6.7%) patients did so in untreated group (Fisher's exact test; P < .0001). Mean total SIP score improved among patients in the treated group compared with patients in untreated group (MANOVA for time and treatment, P=.002). Improvement in HRQOL was related to the improvement in psychometry. Thus treatment with lactulose improves both cognitive functions and HRQOL in cirrhotic patients with MHE.

Prebiotics and Synbiotics

Treatment with synbiotics (probiotics and fermentable fiber) has been suggested but not assessed in controlled studies in the treatment of MHE. Liu, et al[58], reported an alternative and novel approach of modulating the gut microecology and acidifying the gut lumen for therapeutic benefit in cirrhotic patients with MHE by treatment with synbiotics. The investigators of this study have attempted to confirm the usefulness of synbiotics in the treatment of MHE. They screened 97 consecutive cirrhotic patients without overt hepatic encephalopathy (HE) for MHE using the number connection test (NCT) and measurement of BAEP. MHE, defined by abnormality of at least one test modality, was seen in 58 (60%) patients. Fifty-five of them MHE were randomized to receive a synbiotic preparation, i.e. a probiotic plus fermentable fiber (n = 20), fermentable fiber (n = 20), or placebo (n = 15) for 30 days. Probiotic compound consisted of 4 freeze-dried, non-urease-producing bacteria, namely *Pediacoccus pentoseceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* subspecies *paracasei* 19 and Lactobacillus *plantarum* 2592, each at dose of 10^{10} colony forming units per sachet. Fermentable fiber consisted of beta glucan, 2.5 g; inulin 2.5 g, pectin 2.5 g, and resistant starch, 2.5 g. Placebo consisted of wheat based nonfermentable fiber. Patients were evaluated with NCT and BAEP, serum ammonia and endotoxin levels, and stool quantitative bacteriological analysis at study entry, after 1-month of treatment and again after 14 days.

Cirrhotic patients with MHE had substantial derangements in the gut microecology, with significant fecal overgrowth of potentially pathogenic *Escherichia coli* and *Staphylococcal* species. Synbiotic treatment significantly increased the fecal content of non-urease-producing *Lactobacillus* species at the expense of these other bacterial species. The effect persisted at reassessment 14 days after cessation of supplementation. Such modulation of gut flora was associated with a significant reduction in blood ammonia levels and reversal of MHE in 50% of patients. Synbiotic treatment was also associated with a significant reduction in endotoxemia. The Child-Turcotte-Pugh functional class improved in nearly half of patients. Similar benefit was observed with fermentable fiber alone in a substantial proportion of patients. It may be concluded that the treatment with synbiotics or fermentable fiber is an alternative to lactulose for management of MHE in patients with cirrhosis.

Shall we routinely screen cirrhotic patients for the presence and treatment of MHE?[59] Recently published literature favors it.

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. Cadranel JF, Lebiez E, Di Martino V, Bernard B, El Koury S, Tourbah A, Pidoux B, Valla D, Opolon P. Focal neurological signs in hepatic encephalopathy in cirrhotic patients: an underestimated entity? Am J Gastroenterol 2001;96:515-8.
3. Joebges EM, Heidemann M, Schimke N, Hecker H, Ennen JC, Weissenborn K. Bradykinesia in minimal hepatic encephalopathy is due to disturbances in movement initiation. J Hepatol 2003;38:273-80.
4. Amodio P, Del Piccolo F, Petteno E, Mapelli D, Angeli P, Iemmolo R, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol 2001;35:37-45.
5. Elsass P, Christensen SE, Mortensen EL, Vilstrup H. Discrimination between organic and hepatic encephalopathy by means of continuous reaction times. Liver 1985;5:29-34.
6. Ross BD, Jacobson S, Villamil F, Korula J, Kreis R, Ernst T, Shonk T, Moats RA. Subclinical hepatic encephalopathy: Proton MR spectroscopic abnormalities. Radiology 1994;193:457-63.
7. Burra P, Pizzolato G, Orlando F, Rossato A, Chierichetti F, Tedeschi U, et al. Single-photon emission computed tomography with^{99m} TC-hexamethylpropyleneamineoxide in cirrhotic patients before and after liver transplantation. Transplant Proc 1994;26:3677-8.
8. Norenberg, MD. Astrocytic-ammonia interactions in hepatic encephalopathy. Seminars in Liver Disease 1996;16:245-53.
9. Baraldi M, Pinelli G, Ricci P, Zeneroli ML. Toxins in hepatic encephalopathy: the role of the synergistic effect of ammonia, mercaptans and short chain fatty acids. Arch Toxicol Suppl 1984;7:103-5.
10. Wang V, Saab S. Ammonia levels and the severity of hepatic encephalopathy. Am J Med 2003;114: 237-238.

11. Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, Arroliga AC, Mullen KD. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med 2003;114:188-93.
12. Clemmensen JO, Larsen FS, Kondrup J, et al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999;29:648-53.
13. Moroni F, Lombardi G, Moneti G, Cortesini C. The release and neosynthesis of glutamic acid are increased in experimental models of hepatic encephalopathy. J Neurochem1983;40:850-4.
14. Baraldi M, Zeneroli ML. Experimental hepatic encephalopathy: changes in the binding of gamma-amino bulync acid. Science 1982;216:427-29.
15. Zeneroli ML, Baraldi M, Ventura E, Vezzelli C, Tofanetti O, Germini M, Casciarri I. Alterations of GABA-A and dopamine D-2 brain receptors in dogs with portal-systemic encephalopathy. Life Sci 1991;48:37-50.
16. Macdonald GA, Frey KA, Agranoff BW, Minoshima S, Koeppe RA, Kuhl DE, Shulkin BL, Lucey MR. Cerebral benzodiazepine receptor binding in vivo in patients with recurrent hepatic encephalopathy. Hepatology 1997;26:277-82.
17. Avallone R, Corsi L, Zeneroli ML, Baraldi M. Presence of benzodiazepine-like molecules in food and their implication in the nutrition of cirrhotic patients. Inn Food Sc Technol 2001;23:193-98.
18. Basile AS, Harrison PM, Hughes RD, Gu ZQ, Pannelle L, Mckinsety, A, Jones EA, Williams R. Relationship between plasma benzodiazepine receptor ligand concentrations and severity of hepatic encephalopathy. Hepatology 1994;11:112-121.
19. Nielsen K, Kondrup J, Martinsen L, Døssing H, Larsson B, Stilling B, et al. Long-term oral refeeding of patients with cirrhosis of the liver. Br J Nutr 1995;74:557-67.
20. Córdoba J, López-Hellín J, Planas M, Sabín P, Sanpedro F, Castro F. Normal diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41:38-43.
21. Kearns PJ, Young H, Garcia G, Blaschke T, O'Hanlon G, Rinki M, et al. Accelerated improvement of alcoholic liver disease with enteral nutrition. Gastroenterology 1992;102:200-5.
22. Morgan TR, Moritz TE, Mendenhall CL, Haas R, and VA Cooperative Study Group #275. Protein consumption and hepatic encephalopathy in alcoholic hepatitis. J Am Coll Nutr 1995;14:152-8.
23. Plauth M, Merli M, Kondrup J,Weimann A, Ferenci P, Müller MJ. ESPEN Consensus Group. ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr 1997;16:43-55.
24. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004;328:1046-50.
25. Rolachon A, Zarski JP, Lutz JM, Fournet J, Hostein J. [Is the intestinal lavage with a solution of mannitol effective in the prevention of post-hemorrhagic hepatic encephalopathy in patients with liver cirrhosis? Results of a randomized prospective study] Gastroenterol Clin Biol 1994;18:1057-62. French.
26. Festi D, Vestito A, Mazzella G, Roda E, Colecchia A. Management of hepatic encephalopathy: Focus on Antibiotic Therapy. Digestion 2006;73(suppl 1):94-101.
27. Fast BB, Wolfe SJ, Stormont JM, Davidson CS. Antibiotic therapy in the management of hepatic coma. Arch Intern Med 1958;101:467-75.
28. Solga SF, Diehl AM. Gut flora-based therapy in liver disease? The liver cares about the gut. Hepatology 2004;39:1197-1200.
29. Kircheis G, Nilius R, Held C, Berndt H, Buchner M, Gortelmeyer R, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. Hepatology 1997;25:1351-60.
30. Riggio O, Merli M, Capocaccia L, Caschera M, Zullo A, Pinto G, et al. Zinc supplementation reduces blood ammonia and increases liver rnithine transcarbamylase activity in experimental cirrhosis. Hepatology 1992;16:785-9.
31. Sushma S, Dasarathy S, Tandon RK, Jain S, Gupta S, Bhist MS. Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial. Hepatology 1992;16:138-44.
32. Goulenok C, Bernard B, Cadranel JF, Thabut D, Di Martino V, Opolon P, Poynard T. Flumazenil vs. placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis. Aliment Pharmacol Ther 2002;16:361-72.
33. Prasad S, Dhiman RK, Duseja A, Chawla Y, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in cirrhotic patients with minimal hepatic encephalopathy. Hepatology 2007; 45: (In press).
34. Groeneweg M, Quero JC, De Bruijn I, Hartmann IJ, Essink-bot ML, Hop WC, Schalm SW. Subclinical hepatic encephalopathy impairs daily functioning. Hepatology 1998;28:45-49.
35. Schomerus H, Hamster W. Quality of life in cirrhotics with minimal hepatic encephalopathy. Metab Brain Dis 2001;16:37-41.
36. Watanabe A, Tuchida T, Yata Y, Kuwabara Y. Evaluation of neuropsychological function in patients with liver cirrhosis with special reference to their driving ability. Metab Brain Dis 1995;10:239-48.
37. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Dolle W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981;26:622-30.
38. Wein C, Koch H, Popp B, Oehler G, Schauder P. Minimal hepatic encephalopathy impairs fitness to drive. Hepatology 2004;39:739-45.
39. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J Gastroenterol Hepatol 2001;16:531-5.

40. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol 2001;96:2718-23.
41. Hartmann IJ, Groeneweg M, Quero JC, Beijeman SJ, de Man RA, Hop WC, Schalm SW. The prognostic significance of subclinical hepatic encephalopathy. Am J Gastroenterol 2000;95:2029-34.
42. Amodio P, Del Piccolo F, Marchetti P, Angeli P, Iemmolo R, Caregaro L, et al. Clinical features and survivial of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. Hepatology 1999;29:1662-7.
43. Romero-Gomez M, Grande L, Camacho I, Benitez S, Irles JA, Castro M. Altered response to oral glutamine challenge as prognostic factor for overt episodes in patients with minimal hepatic encephalopathy. J Hepatol 2002;37:781-7.
44. Romero-Gomez M, Grande L, Camacho I. Prognostic value of altered oral glutamine challenge in patients with minimal hepatic encephalopathy. Hepatology 2004;39:939-43.
45. Kharbanda PS, Saraswat VA, Dhiman RK. Minimal hepatic encephalopathy: diagnosis by neurophchological and neurophysiological methods; Indian J Gastroenterol 2003;22:{Suppl 2}537-41.
46. Ortiz M, Jacas C, Cordoba J. Minimal hepatic encephalopathy: diagnosis, clinical significance and recommendations. J Hepatol 2005; 42 Suppl(1):S45-53.
47. Van der Rijt CDC, Schalm S, De Groot GH, De Vlieger M. Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroenceph Clin Neurophysiol 1984;57:423-26.
48. Amodio P, Marchetti P, Del Piccolo F, de Tourtchaninoff M, Varghese P, Zuliani C, et al. Spectral versus visual EEG analysis in mild hepatic encephalopathy. Clin Neurophysiol 1999;110:1334-134.
49. Senzolo M, Amodio P, D'Aloiso MC, Fagiuoli S, Del Piccolo F, Canova D, et al. Neuropsychological and neurophysiological evaluation in cirrhotic patients with minimal hepatic encephalopathy undergoing liver transplantation. Transplant Proc 2005;37:1104-7.
50. Saxena N, Bhatia M, Joshi YK, Garg PK, Dwivedi SN, Tandon RK. Electrophysiological and neuropsychological tests for the diagnosis of subclinical hepatic encephalopathy and prediction of overt encephalopathy. Liver 2002;22:190-7.
51. Balata S, Damink SW, Ferguson K, Marshall I, Hayes PC, Deutz NE, et al. Induced hyperammonemia alters neuropsychology, brain MR spectroscopy and magnetization transfer in cirrhosis. Hepatology 2003;37:931-9.
52. Cordoba J, Alonso J, Rovira A, Jacas C, Sanpedro F, Castells L, et al. The development of low-grade cerebral edema in cirrhosis is supported by the evolution of (1)H-magnetic resonance abnormalities after liver transplantation. J Hepatol 2001;35:598-604.
53. Lockwood AH, Yap EW, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J Cereb Blood Flow Metab 1991;11:337-41.
54. de Bruijn KM, Blendis LM, Zilm DH, Carlen PL, Anderson GH. Effect of dietary protein manipulation in subclinical portal-systemic encephalopathy. Gut 1983;24:53-60.
55. Egberts EH, Schomerus H, Hamster W, Jurgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. A double-blind placebo-controlled crossover study. Gastroenterology 1985;88: 887-95.
56. Dhiman RK, Sawhney MS, Chawla YK, Das G, Ram S, Dilawari JB. Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy. Dig Dis Sci 2000;45:1549-52.
57. Watanable A, Sakai T, Sato S, et al. Clinical efficacy of lactulose in cirrhotic patients with and without subclinical hepatic encephalopathy. Hepatology 1997;26:1410-14.
58. Liu Q, Duon ZP, Ha DK, et al. Symbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with corrhosis. Heptology 2004;39:1441-49.
59. Dhiman RK, Chawla YK. Minimal Hepatic Encephalopathy: Should we start treating it? Gastroenterology 2004;127:1855-7.