Hepatic Encephalopathy: High Lights

Gadour M O EH[1], Al kalaefa M S[1]

Introduction

Hepatic encephalopathy (HE) remains a challenge to hepatologists. It is defined as a protean spectrum of potentially reversible neuropsychiatric abnormalities developing in patients with hepatic dysfunction and or portal hypertension after exclusion of brain disease and/or unrelated metabolic abnormalities. Considerable difficulties arise when applying this definition to patients whose basic disease affects the brain as well as the liver e.g. Wilson's and ethanol induced liver disease. Overt HE is common, and is reported to affect 30-45% of cirrhotic patients.[1, 2]

HE is characterized by disturbances of personality, intelligence, level of consciousness, extrapyramidal and motor activity. Diversion of the blood –loaded with neurotoxic substances- away from the detoxifying hepatocytes either through spontaneous or induced shunts or because of paucity of normal hepatocytes is a corner stone in the development of HE. However, neither the presence nor the severity of the liver disease (Child's classification) or portal hypertension has a strong or consistent relationship with the development of this disease. This highlights the essential role of other factors in the pathogenesis of HE.

A lot of research was done to explore the nature of the disease and many hypotheses came out. Nevertheless, the exact mechanisms underlying the development of the clinical symptoms of HE remain far from precise identification[3, 4]. This added to the difficulties in evaluation and management of these patients.

Clinical manifestations

Beside the clinical features of the underlying liver disease and/or portal hypertension, patients with HE usually have cognitive, extra pyramidal and motor dysfunction. HE is considered to be the hallmark of fulminant hepatic failure (FHF) when it is associated with an acute elevation of liver enzymes.

Depending on chronicity and/or the presence of portal hypertension the 11th World Congresses of Gastroenterology typed HE as follows[5, 6]:

Type A: HE associated with acute liver failure.

Type B: HE associated with portosystemic bypass (non-cirrhotic).

Type C: HE associated with chronic liver disease/cirrhosis. This was further sub-classified to:

Episodic HE: single or recurrent.
Persistent HE: mild or severe.
Minimal HE(MHE): formerly called subclinical or latent.

Any of these types may present with different features denoting degrees of severity which is the bases for staging the HE into five stages. (The table)[7].

These features if present together will justify staging, otherwise they are neither specific nor diagnostic of the stage and on many occasions they may overlap. Disturbances in the diurnal sleep pattern usually preceed overt HE. Flapping tremors which are commonly tested for are not pathogenomic of the disease and can be seen in almost all end stage organ failures. Some features including restlessness, agitation, irritability, lethargy, forgetfulness, apraxia, incoordination and others may be present with variable degrees.

Patients with HE may present with focal neurological signs especially hemiplegia.[8]. Diffuse or focal seizures can unmask HE. Their incidence is unknown. On rare occasions patients with HE may present with status epilepticus. [9-12]

It was initially believed that cerebral function is normal in the interval between episodes of HE; this turned to be incorrect when more sensitive diagnostic tests such as the new psychometric and neurophysiological assessment were applied. Also before the first episode of overt HE, cerebral function may be abnormal. This evidence supports the existence of minimal HE[13-17]

Unlike minimal HE, stages 1-4 are usually overt and pauses no diagnostic difficulties

1. Assoc. Prof. of Medicine. Department of Medicine. Omdurman Islamic University. Khartoum, Sudan.
Correspondence;
Dr. M O EH Gadour. Ibn Sina Hospital. Khartoum, Sudan.Email: mgadour@hotmail.com

Table: Some of the common features of each stage of HE (Adapted from Riordan S M and Williams R) [7].

Stage	Level of consciousness	Intellect	Neuro. signs	EEG
Minimal	Normal	Normal	Abnormal psychometric tests	◊ Normal
1	Inverted sleep pattern	forgetfullness	Flapping tremors, impaired handwriting	Triphasic waves
2	* Slow response	* Disorientation for time	Hypotonia, hyporeflexia	Triphasic waves
3	*Somnolence, confusion	* Disorientation for place	Rigidity,hyper-reflexia, Babinski sign	Triphasic waves
4	coma	none	Decerebration	Delta waves

* in addition to the features of previous stage
◊ Abnormal other neuroelectrical tests

Currently hepatologists are giving more weight to MHE as it has therapeutic and prognostic value. Its prevalence in patients with hepatic cirrhosis ranges between 30-84%. This wide range reflects the difficulties in identifying the exact clinical and investigational parameters for diagnosis of this entity. MHE refers to the disturbances in cognitive function, fine concentration requiring motor skills, psychomotor speed, tracking, visuospatial, electrophysiological parameters, cerebral neurochemical/ neurotransmitter homeostasis, cerebral blood flow and fluid homeostasis that may be observed in patients with cirrhosis and/or portal hypertension who have no clinical evidence of hepatic encephalopathy. The frequently used paper-pencil tests are not sensitive enough to diagnose MHE but critical flicker frequency is giving promising results. The psychometric hepatic encephalopathy score has been recommended as the "gold standard" in the diagnosis of MHE. Interestingly the verbal memory skills are relatively well preserved in these patients.[6, 15, 18 -24].

Pathogenesis

The pathogenesis of HE is not well known. There is a consensus that HE is a multifactorial metabolic encephalopathy.[25]. Some theories exist to explain the condition. The most popular ones are related to ammonia, gamma-aminobutyric acid (GABA), false neurotransmitters and others. Overt brain edema and increased intracranial pressure although characteristic of FHF, are also reported to occur in patients with liver cirrhosis. Astrocyte swelling is a characteristic pathological finding in HE and is thought of as the major structural marker of the disease.

However, other factors including gene disturbance, putative neurotoxins including short-chain fatty acids, mercaptans, manganese, hyponatremia, glutamate and ligands of the peripheral benzodiazepine receptor may have a synergistic effect on the event. On the other hand, reactive nitrogen and oxidant compounds are considered to play a major role in HE. Contradicting opinions exist regarding the role of nitric oxide and tumor necrosis factor alpha. There is growing evidence that osmotic and oxidative stresses are closely interrelated. It was suggested recently that inflammation and its modulators may play a synergistic role with ammonia in the pathogenesis of hepatic encephalopathy.[26-30]

Ammonia

About 10% of patients with significant encephalopathy have normal serum ammonia levels and some patients with significant elevation of ammonia have no evidence of HE. This questions the theory of ammonia. Despite this debate ammonia remains to be the major suspect as the injurious substance to the brain. Glutamine is reported to play a crucial role in transferring ammonia from the cytoplasm to the mitochondria of the astrocyte. This glutamine-derived ammonia within mitochondria is thought of as responsible for triggering excessive production of free radicals and induction of the mitochondrial permeability transition leading to astrocyte swelling and dysfunction[31]. The gastrointestinal tract is a major source of ammonia mainly via production by enterocytes from glutamine and only partially by colonic bacterial catabolism of nitrogenous sources in the gut. This is usually detoxified by the liver and the muscles and excreted through the kidneys [29].

Increased ammonia production

Excess dietary protein intake, gastrointestinal hemorrhage, constipation, increased muscle catabolism due to reduced in take, infections, septicemia, blood transfusion, surgical intervention and hypokalemia augment

the production of ammonia. Although skeletal muscles remove more ammonia from the circulation than the cirrhotic liver and incorporate it in the formation of glutamine, they counter act that by releasing the glutamine in the circulation which is taken by the entrocytes and kidneys to reproduce ammonia. Renal ammoniagenesis seems to have an appreciable role in the pathogenesis of HE [32].

Reduced ammonia metabolism

Patients with liver cirrhosis have no adequate viable and functioning hepatocytes to deal with the ammonia coming through the portal system. At the same time these patients have reduced muscle bulk so the other major detoxifying organ is defective. Arterial hypotension, anemia, hypoxemia, fluid restriction, fluid loss through diuretics or diarrhea result in hepatic hypoxemia and so contribute tremendously to the reduction of ammonia removal. Ammonia may bypass the liver though spontaneous or surgical shunts including transjugular intrahepatic portosystemic shunt. A normal ammonia load in these patients will there fore cause significant rise of its level in the circulation.

Increased diffusion of ammonia across blood–brain barrier

Hypokalemia and systemic extracellular alkalosis with intracellular acidosis which are commonly seen in patients with liver cirrhosis disturb the blood brain barrier and increase its permeability to ammonia[33].

GABA- benzodiazepine

Gamm-aminobutyric acid (GABA) is a neuroinhibitory substance produced in the gastrointestinal tract. Under the effect of ammonia the levels of some neurosteroids -which are potent GABA agonists- are increased[26]. Alterations of GABAergic neurotransmission and tone are observed in HE. It is suggested that the increased brain concentration of endogenous ligands on GABA-A receptors rather than disturbance of the integrity of the receptors is responsible for this effect[34].

Patients with HE were found to have altered benzodiazepine metabolism with hypersensitivity and increased tone of the benzodiazepine receptors. Increased benzodiazepine receptor ligands may also participate in the increased GABAergic receptors tone[35].

False-neurotransmitter hypothesis

Other neurotransmitters including histamine 1 receptor agonist were shown in animal trials to participate in the onset of HE. False neurotransmitters such as tyramine, octopamine, and beta-phenylethanolamines were considered to induce HE in appropriate settings[36].

Others

Nitric Oxide

Nitric oxide (NO) is a neurotransmitter and neuromodulator that is found in different body tissues. It dilates the cerebral vasculature and is found to affect the blood brain barrier permeability [37, 38]. Its existence and regulatorty effect in the mitochondria of different brain regions was observed. Mitochondrial dysfunction with decreased nitric oxide activity and expression were reported in animals with hepatic encephalopathy. Clear participation of NO in the pathogenic process of HE was reported in animal models [39 , 40]. Because NO facilitates the systemic hypotension, some believe that by so doing NO will augment hepatic hypoperfusion and hepatocyte hypoxic damage. However, trials on animals to inhibit NO contradict this hypothesis[41].

Zinc and manganese

The extrapyramidal manifestation of HE were attributed to the impaired neuronal oxidative metabolism induced by manganese deposition in the basal ganglia. This is supported by the T1-weighted magnetic resonance imaging (MRI) in cirrhotic patients[42, 43].

Zinc is an essential trace element which has an antioxidant effect. Its deficiency is commonly seen in patients with liver cirrhosis and on occasions is associated with GABAneric receptor disorder [44].

Diabetes and Endotoxins

It had been noted that diabetic patients who have liver cirrhosis have more severe HE without obvious precipitating factors, and if the diabetes is associated with HCV infection, the patient will be prone to express severe HE at an earlier stages of biochemical decompensation. The gastroparesis, intestinal dysmotility and autonomic disturbances associated with diabetes may enhance enteric bacterial overgrowth, increased ammonia production and hence explain the increased severity of HE in these patients[45, 46]. Although it was claimed that endotoxins play significant role in HE the data to support this is scanty and there is no published work to show the effect of endotoxin neutralization on HE. In fact recent reports refute this [47].

Diagnosis

Diagnosis and staging of overt HE is generally a clinical procedure. Simple blood

testing and radiological examination may be helpful in determining the presence and severity of liver disease and/or portal hypertension, unclosing some of the precipitating factors and planning the management program. However, they play no role in the diagnosis of HE.

Determination of ammonia level is needed in only few conditions as it is not required for screening or the diagnosis of HE. It is not an indicator of severity and has no prognostic value. Serial ammonia measurements are inferior to clinical assessment in follow up of patient under therapy for hepatic encephalopathy. Venous and arterial blood ammonia levels are different. However, this has no clinical implication. Only gaseous ammonia which is readily diffusible through the blood-brain barrier is useful for clinical studies and its testing is not available for routine clinical use [48].

Electrophysiologic tests –

Neurophysiologic measures like visual and automatic electroencephalogram (EEG) analysis and spectral EEG[49] may add to the staging of HE, whereas, checker board and flash visual evoked potentials, brainstem auditory-evoked potentials, somatosensory-evoked potentials, [50] and Critical flicker frequency(CFF) [51] are part of the diagnostic tool for MHE .

Alteration in the CFF threshold was reported to serve as a diagnostic marker for hepatic encephalopathy[51, 52].

These neuropsychometric tests may not readily return to normal after improvement of HE and even after liver transplant. This raises the possibility that these tests may be assessing different components of HE. [53].

Conventional Computed tomography and magnetic resonance imaging of the brain are of use if the diagnosis of HE is questionable and for determination of other related brain complications. T1 mapping with partial inversion recovery may be helpful in determining HE severity [54].

Treatment

General measures:

Because it is reversible and on occasions episodic, spontaneous recovery is expected in a high percentage of patients. However, those who do not have this favorable outcome usually require in hospital management. Correction of the precipitating factor- if possible- is the most important measure. Those with stage three and four HE have to be treated in intermediate or intensive care units. Because of the systemic hypotension and hypoxemia seen in these patients oxygen supplementation should be given. Close observation for the three common killers in HE- hypoglycemia, cerebral edema and infection- and prompt treatment of them is of atmost importance. Also it is important to observe for the significant unpleasant side effects of the classical treatment of HE which may include diarrhea, renal failure, neuropathy and other gastrointestinal disturbances. Sedatives should be avoided whenever possible.[55, 56].

Special measures

Diet

Patients with liver cirrhosis have reduced stores of vitamins and glycogen and are prone to hypoglycemia. On the other hand liver content of iron is usually high. Diet rich in carbohydrates and vitamins is advocated. Restriction of protein intake especially animal proteins was the rule in the treatment of HE for quite a long time. This had gradually changed as catabolization of the patients' own proteins and worsening of their condition were noticed. Recently a lot of debate came out questioning the validity of protein restriction and some advocate diet with normal protein content to patients with HE especially those who have the episodic type. Proteins have to be calculated and administered in a precise way that will neither lead to over load nor augment internal catabolism. Diets with high vegetable proteins were shown to have favorable impact on patients with HE [57-60].

Disaccharides

Despite being a constant item in the treatment of HE; the use of oral non-absorbable disaccharides like lactulose and lactitol was also recently questioned. Review of randomized trials neither supported nor refuted their usage. However, lactulose enema was proved effective in treatment of HE. [61].

Antibiotics

Antibiotics are essential for treatment of precipitating or co-existing infection in patients with HE. Oral antibiotics "to sterilize the bowel" were found to be superior to oral disaccharides in treatment of the encephalopathy. Rifaximin is reported to be more effective and safe alternative to some of the currently used oral drugs especially in patients with impaired renal function. Interestingly some studies claimed that eradication of H. pylori may be helpful for prevention and treatment of HE[62-64].

Dialysis

Continuous venovenous hemodiafiltration, intermittent dialysis and plasmapheresis were found to be helpful in ameliorating the impact of

rapid fluid shifts and remove some neurotoxins from the circulation. Some types of albumin dialysis had shown promising results regarding survival in FHF and other types of HE. Because of their inherently limited role, these measures were suggested as supportive therapy options in combination with standard treatment in HE[65-67].

Others

Elevation of the head of the bed to 30 degrees to improve venous drainage and use of intravenous mannitol may help to reduce cerebral edema.[68].

Trails on animals had shown that induced hypothyroidism and marginal hypothermia via reduction of metabolism and amelioration of the hyerdynamic circulation in patients with liver cirrhosis may reduce oxidative liver injury and be beneficial in treatment of HE [69].

By improving antioxidant defenses, C-Phycocyanin is potentially effective in patients with HE[70]. L-ornithine and L-aspartate were found to stimulate and increase the activity of glutamine synthetase and hence reduce ammonia level in patients with liver cirrhosis.[71].

Synbiotics, fermentable fiber and L-Acetylcarnitine were reported to improve the clinical picture in some patients. On the other hand flumazenil which had gained initially a lot of enthusiasm in treatment of HE was reported later to be effective in only a small minority of patients [72 -74].

None responders:

Patients who show no response or an unexpected sub-optimal response to treatments should be reviewed. Especial consideration for hidden complications is important. These include occult infection, trace mineral deficiency, bowel ischemia and large spontaneous portosystemic shunts and others which are potentially amenable to treatment[61].

Intermittent therapy with an extracorporeal liver support system seemed to sufficiently replace hepatic detoxification on a long-term basis in some patients and may be a good tool to bridge the time period until liver transplantation which so far remains to be the gold standard treatment for HE [75].

Prognosis

Development of HE is an independent poor prognostic factor in patients with liver cirrhosis with 1-year mortality rate of about 60%. Elevated liver enzymes, low serum albumin, evidence of renal failure are independent risk factors for poor prognosis [55, 76].

References

1. Amodio P, Del Piccolo F, Petteno E, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol 2001; 35: 37–45.
2. Romero-Gomez M, Boza F, Garcia- Valdecasas MS, et al. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol 2001; 96: 2718–23.
3. Butterworth RF. The neurobiology of hepatic encephalopathy. Semin Liver Dis 1996;16:235-244.
4. Butterworth RF. Complications of cirrhosis III. Hepatic encephalopathy. J Hepatol 2000;32:171-180.
5. Ong JP, Mullen KD. Hepatic encephalopathy. Eur J Gastroenterol Hepatol 2001;13:325-334.
6. Ferenci P, Lockwood A, Mullen K et al. 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: 716-721.
7. Riordan S M and Williams R. Treatment of Hepatic Encephalopathy. NEJM 1997; 337 (7): 473-79
8. Cadranel JF, Lebiez E, Di Martino V et al. Focal neurological signs in hepatic encephalopathy in cirrhotic patients: An underestimated entity? Am J Gastroenterol 2001; 96: 515-8
9. Ficker DM, Westmoreland BF, Sharbrough FW. Epileptiform abnormalities in hepatic encephalopathy. J Clin Neurophysiol 1997; 14:230–4.
10. Plum F, Posner JB. Diagnosis of stupor and coma, 3rd edn. Philadelphia: FA Davis, 1980.
11. Annoni JM, Giostra E, Goumaz M, et al. Focal hepatic encephalopathy with status epilepticus. Incomplete recovery after hepatic transplantation. Dig Dis Scie 1997;42:792–5.
12. Delanty N, French JA, Labar DR, et al. Status epilepticus arising de novo in hospitalized patients: an analysis of 41 patients. Seizure 2001; 10:116–9.
13. Gitlin N. Subclinical portal-systemic encephalopathy. Am J Gastroenterol 1988;82:8-11.
14. Quero JC, Hartmann IJC, Meulstee J, et al. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. Hepatology 1996;24:556-560.
15. McCrea M, Cordoba J, Vessey G, et al. Neuropsychological characterization and detection of subclinical hepatic encephalopathy. Arch Neurol 1996;53:758-763.
16. Gitlin N, Lewis DC, HinMey L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy ambulant, non-shunted patients with cirrhosis. J Hepatol 1986;3:75-82.

17. Amodio P, Quero JC, Del Piccolo F, et al. Diagnostic tests for the detection of subclinical hepatic encephalopathy: Comparison of standard and computerized psychometric tests with spectral-EEG. Metab Brain Dis 1996; 1: 31 1 5-328.
18. Montoliu C, Piedrafita B, Serra MA, et al.Activation of soluble guanylate cyclase by nitric oxide in lymphocytes correlates with minimal hepatic encephalopathy in cirrhotic patients. J Mol Med 2007 Mar; 85(3):233-41.
19. Torre Delgadillo A, Guerrero-Hernandez I, Uribe M. Minimal hepatic encephalopathy: characteristics, diagnosis and clinical implications. Rev Gastroenterol Mex 2006 Jan-Mar; 71(1):63-70.
20.. Haussinger D. Hepatic encephalopathy. Schweiz Rundsch Med Prax 2006 Oct 4;95(40):1543-9
21. Schomerus H, Hamster W. Neuropsychological aspects of portalsystemic encephalopathy. Metab Brain Dis 1998;134:361–377.
22. Lockwood AH. "What's in a name?" Improving the care of cirrhotics. J Hepatol 2000;32:859–861.
23. Weissenborn K, Ennen JC, Schomerus H, et al. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34:768–773.
24.Butterworth RF. Hepatic encephalopathy: a neuropsychiatric disorder involving multiple neurotransmitter systems. Curr Opin Neurol 2000; 13:721–727.
25 Jones EA. Ammonia, the GABA neurotransmitter system, and hepatic encephalopathyMetab Brain Dis. 2002 Dec; 17(4):275-81
26. Ahboucha S; Butterworth RFNeuroscience. Pathophysiology of hepatic encephalopathy: a new look at GABA from the molecular standpoint. Metab Brain Dis. 2004; 19(3-4):331-43 .
27. Jalan R, Dabos K, Redhead DN, et al. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. J Hepatol 1997;27:928-933.
28. Schliess F, Gorg B, Haussinger D. Pathogenetic interplay between osmotic and oxidative stress: the hepatic encephalopathy paradigm. Biol Chem. 2006 Oct-Nov; 387: 1363-70.
29. Wright G, Jalan R. Management of hepatic encephalopathy in patients with cirrhosis. Best Pract Res Clin Gastroenterol 2007; 21(1):95-110.
30. Bernal W, Donaldson P, Underhill J, et al. Tumor necrosis factor genomic polymorphism and outcome of acetaminophen (paracetamol)-induced acute liver failure. J Hepatol 1998; 29: 53–9.
31. Albrecht J, Norenberg MDGlutamine: a Trojan horse in ammonia neurotoxicity. Hepatology 2006 Oct; 44(4):788-94.
32. Olde Damink SW, Jalan R, Redhead D Net al. Interorgan ammonia and amino acid metabolism in metabolically stable patients with cirrhosis and a TIPSS. Hepatology Nov 2002;1163-1171
33. Lockwood AH, Finn RD, Campbell JA, et al. Factors that affect the uptake of ammonia by the brain: the blood-brain pH gradient. Brain Res 1980;181: 259-266.
34. Ahboucha S, Butterworth RF. Role of Endogenous Benzodiazepine Ligands and Their GABA-A-Associated Receptors in Hepatic Encephalopathy. Metab Brain Dis 2005 Dec; 20(4):425-37.
35.Pietro Cortellia, Rossella Avallonec, Mario Baraldic, et al Endozepines in recurrent stupor. Sleep Medicine Reviews 2005; 9: 477-487.
36 Schwartz, JC, Arrang JM, Garbarg M, et al Histaminergic transmission in the mammalian brain. Physiol Rev 1991; 71: 1-51.
37. Janigro D, West GA, Nguyen TS, et al. Regulation of blood- brain barrier endothelial cells by nitric oxide. Circ Res 1994;75: 528-38.
38. Jaworowicz DJ, Korytko PJ, Lakhman SS, et al. Nitric oxide and prostaglandin E2 formation parallels blood-brain barrier disruption in an experimental rat model of bacterial meningitis. Brain Res Bull 1998; 46: 541-6.
39. Bustamante J,Czerniczyniec A, Lores-Arnaiz S. Brain nitric oxide synthases and mitochondrial function. Front Biosci 2007 Jan 1; 12: 1034-40.
40. Suarez I, Bodega G, Arilla E, et al. The expression of nNOS, iNOS and nitrotyrosine is increased in the rat cerebral cortex in experimental hepatic encephalopathy. Neuropathol Appl Neurobiol 2006 Dec; 32(6):594-604.
41. Chu C.-J., Wang S.-S., Lee F.-Y., et al .Detrimental effects of nitric oxide inhibition on hepatic encephalopathy in rats with thioacetamide-induced fulminant hepatic failure. European Journal of Clinical Investigation 2001; 31: 156-163.
42. Pujol A, Pujol J, Graus F, et al. Hyperintense globus pallidus on T1-weighted MRI in cirrhotic patients is associated with severity of liver failure. Neurology 1993;43:65–9
43. Butterworth RF, Spahr L, Fontaine S, et al. Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. Metabolic Brain Dis 1995;10:259 –67.
44. Chetri K, Choudhuri G. Role of trace elements in hepatic encephalopathy: zinc and manganese. Indian J Gastroenterol 2003 Dec;22 Suppl 2:S28-30.
45. Abrahamsson H. Gastrointestinal motility disorders in patients with diabetes mellitus. J Intern Med 1995;237:403–9.
46. Spengler U, Stellaard F, Ruckdeschel G, et al. Small intestinal transit, bacterial growth, and bowel habits in diabetes mellitus. Pancreas 1989;4:65–70.
47 Chen CT, Chu CJ, Wang TF, et al. Evidence against a role for endotoxin in the hepatic encephalopathy of rats with thioacetamide-induced fulminant hepatic failure. J Gastroenterol Hepatol 2005 Mar;20(3):450-5.

48. Kramer L, Tribl B, Gendo A et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatolog 2000;31: 30-4
49 Amodio p, Marchetti P, Del Piccolo F et al. Spectral versus visual EEG analysis in mild hepatic encephalopathy. Clin Neurophysiol 1999; 110:1334-44.
50 Kullmann F, Hollerbach S, Holstege A et al. Subclinical hepatic encephalopathy: The diagnostic value of evoked potentials. J Hepatol 1995; 22: 101-10
51. Kircheis G, wettstein M, Timmermann 1 et al. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. Hepatology 2002; 35: 357-66
52. Weissenborn K. Minimal Hepatic Encephalopathy: A Permanent Source of Discussion. Hepatoplogy 2002; 35(2):494-496
53. Ciancio A, Marchet A, Saracco G et al. Spectral Electroencephalogram Analysis in Hepatic Encephalopathy and Liver Transplantation. Liver Transplantation 2002; l8(7): 630-635 .
54. Shah NJ, Neep H, Zaitsev M et al. Quantitative T1 mapping of hepatic encephalopathy using magnetic resonance imaging. Hepatology 2003; 38: 1219-26
55. Dbouk N, McGuire BM. Hepatic encephalopathy: a review of its pathophysiology and treatment. Curr Treat Options Gastroenterol 2006 Dec;9(6):464-74.
56. Blei AT; Cordoba J. Hepatic Encephalopathy. Am J Gastroenterol 2001; 96(7):1968-76.
57. Heyman JK, Whitfield CJ, Brock KE, et al. Dietary protein intakes in patients with hepatic encephalopathy and cirrhosis: current practice in NSW and ACT. Med J Aust 2006;185(10):542-3.
58. Cordoba J, Lopez-Hellin J, Planas M, Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004; 41(1):38-43.
59. Heidelbaugh JJ, Sherbondy M.Cirrhosis and chronic liver failure: part II. Complications and treatment. Am Fam Physician 2006 Sep 1;74(5):781. .
60. Weber FL, Minco D, Fresard K et al. Effects of vegetable diets on nitrogen metabolism in cirrhotic subjects. Gastroenterology1985; 89: 538–44.
61. Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004; 328: 1046–51.
62. Miglio F, Valpiani D, Rossellini SR et al. Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomised trial. Curr Med Res Opin 1997; 13(10):593-601
63. Mas A, Rodes J, Sunyer L, Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. Hepatology 2003 Aug;38(2):527-8.
64. Wang LJ, Cai JT, Chen T, et al. The effects of Helicobacter pylori infection on hyperammonaemia and hepatic encephalopathy in cirrhotic patients. Zhonghua Nei Ke Za Zhi 2006 Aug;45(8):654-7
65. Ozdemir FN, Tutal E, Sezer S, et al.Effect of supportive extracorporeal treatment in liver transplantation recipients and advanced liver failure patients. Hemodial Int 2006 Oct;10 Suppl 2:S28-32.
66. Moragues Ribes C, Cases Viedma E, Ruano Marco M. Albumin dialysis in patients with acute exacerbation of chronic liver failure in an intensive care unit. Med Clin (Barc) 2006 Nov 4;127(17):641-4
67. Davenport A, Will EJ, Davison AM. Effect of posture on intracranial pressure and cerebral perfusion pressure in patients with fulminant hepatic and renal failure after acetaminophen self-poisoning. Crit Care Med 1990;18:286-289.
68. Wong F. J. Drug insight: the role of albumin in the management of chronic liver disease. Nat Clin Pract Gastroenterol Hepatol 2007 Jan;4(1):43-51.
69. Chang CC, Chen YC, Huang HC, et al. Methimazole alleviates hepatic encephalopathy in bile-duct ligated cirrhotic rats. J Chin Med Assoc 2006 Dec; 69(12):563-8.
70. Sathyasaikumar KV, Swapna I, Reddy PV, et al.Co-administration of C-Phycocyanin ameliorates thioacetamide-induced hepatic encephalopathy in Wistar rats. J Neurol Sci 2007 Jan;252(1):67-75
71. Rose C, Michalak A, Rao KV, et al. 1-ornithine-L-aspartate lowers plasmaand cerebrospinal fluid ammonia and prevents brain edema in rats with acute liver failure. Hepatology 1999; 30:636–40.
72 Malaguarnera M, Pistone G, Astuto M, et al. Effects of L-acetylcarnitine on cirrhotic patients with hepatic coma: randomized double-blind, placebo-controlled trial. Dig Dis Sci 2006 Dec; 51(12):2242-7.
73. Qing Liu, Zhong Ping Duan, Da Kang Ha, et al Synbiotic Modulation of Gut Flora: Effect on Minimal Hepatic encephalopathy in Patients with Cirrhosis. Hepatology 2004; 39(5): 1441-1449.
74. Barbaro G, Dilorenzol G, Soldini M, et al. Flumazenil for Hepatic Encephalopathy Grade III and Iva in Patients With Cirrhosis: An Italian Multicenter Double-Blind, Placebo-Controlled, Cross-Over Study. Hepatology1998; 28(2): 374-378.
75. Jung O, Asbe-Vollkopf A, Betz C, et al. Long-Term Bridging of Acute on Chronic Liver Failure to Successful Transplantation with an Extracorporeal Liver Support System. Z Gastroenterol 2007 Jan; 45(1):21-24
76. Poordad FF. Review article: the burden of hepatic encephalopathy Aliment Pharmacol Ther 2007 Feb;25 Suppl 1:3-9.