Hepatic Encephalopathy

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ABSTRACT

Hepatic encephalopathy is a severe complication of cirrhosis that is related to the effects of ammonia. Analysis of interorgan ammonia trafficking has identified an important role of skeletal muscle in ammonia removal and has highlighted the importance of the nutritional status. Ammonia causes neurotransmitter abnormalities and induces injury to astrocytes that is partially mediated by oxidative stress. These disturbances lead to astrocyte swelling and brain edema, which appear to be involved in the pathogenesis of neurological manifestations. Inflammatory mediators worsen brain disturbances. New methods for assessing hepatic encephalopathy include clinical scales, neuropsychological tests, imaging of portal-systemic circulation, and magnetic resonance of the brain. Reappraisal of current therapy indicates the need for performing placebo-controlled trials and the lack of evidence for administering diets with restricted protein content. Liver transplant should be considered in selected patients with hepatic encephalopathy. Future prospects include new drugs that decrease plasma ammonia, measures to reduce brain edema, and liver-support devices.

KEYWORDS: Hepatic encephalopathy, ammonia, pathogenesis, diagnostic methods, therapy

Hepatic encephalopathy (HE) is a frequent and serious complication of cirrhosis that carries prognostic implications. In recent years, we have witnessed important achievements in the management of the complications of cirrhosis, which are reviewed in this issue of *Seminars in Liver Disease*. This progress has been the consequence of a better understanding of their pathophysiology. Several investigators have tried to match these achievements in the field of HE. The research has been focused on a reanalysis of ammonia metabolism, applying developments of neuroscience in the study of its pathogenesis, better delineation of the clinical presentation, new diagnostic tools, and a critical reappraisal of available therapies, including nutrition and liver transplant. In this article we will review the most significant progress in each of these aspects.

PATHOGENESIS

The two elements that confer the name to the syndrome and intervene in its clinical classification are neurological disturbance and liver failure. According to the characteristics of the neurological manifestations, HE is classified as episodic (previously acute), persistent (previously chronic), or minimal (previously subclinical).[1] Depending on the disease of the liver, HE is termed type C (associated with cirrhosis), type A (associated with acute liver failure), or type B (associated with portal-systemic bypass and no intrinsic liver disease). Irrespective of the characteristics of the neurological manifestations and the type of liver disease, the link between them is that HE is caused by the effects on the brain of substances that under normal circumstances are efficiently metabolized by the liver.[2] Ammonia remains as the most important

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factor in the pathogenesis of HE. Currently, there is a better explanation of the mechanisms by which ammonia interferes with brain function and a better recognition of the factors that influence these effects.

Ammonia

The association between ammonia neurotoxicity and HE was first suggested by studies in dogs that underwent portal-cava anastomosis (Eck's fistula) and developed neurological manifestations when fed meat.[3] Ammonia is generated in the intestines from different sources: nitrogenous components of the diet, deamination of glutamine, and breakdown of urea by urease present in colonic flora.[4] These features have been known for many years and have been the basis for designing treatments for HE based on the modulation of intestinal generation of ammonia (Fig. 1). Glutaminase, the enzyme that metabolizes the deamination of glutamine, has been thought to play an important role in the pathogenesis of HE.[5] In the intestines, the activity of glutaminase has been associated with minimal HE, probably because it regulates the generation of ammonia.[6] Neomycin, a drug that improves HE, may act by inhibiting intestinal glutaminase.[7] In the brain, glutaminase is located in the mitochondria of astrocytes and might be implicated in the toxic effects of ammonia in this organelle.[8]

Interorgan ammonia trafficking has been quantified in cirrhotic patients.[9] The relative contribution of different organs highlights the role of skeletal muscle to buffer ammonia that is produced in the intestines and is not metabolized in the liver. These data suggest that favoring an anabolic metabolic state may decrease ammonia concentration in the blood. A negative protein balance has been shown in advanced cirrhosis.[10] This balance can be partially reversed in different clinical situations. Isoleucine infusions promote protein synthesis after gastrointestinal bleeding,[11] anabolic steroids improve nutritional status in moderately malnourished patients with acute alcoholic hepatitis,[12] and a diet with normal protein content avoids the increased protein breakdown seen in patients with episodic HE treated with low-protein diets.[13] Malnourishment, which traditionally has been linked to a worse clinical outcome in cirrhosis, may be difficult to combat through diet interventions.[14] Branched chain amino acids may be helpful for this purpose, because they promote protein synthesis.[15] The administration of branched chain amino acids-enriched diets may slow the progression of cirrhosis[16] and through this mechanism improve persistent HE.[17]

The kidney is another organ that is important in regulating blood ammonia levels. An increase in the generation of ammonia in the kidney has been shown after gastrointestinal bleeding[18] and may follow dehydration and the administration of diuretics. Expansion of plasma volume, a common practice in patients with episodic HE, increases the excretion of urea in the urine and may be helpful to shorten the duration of HE.[19]

A common criticism of the role of ammonia in HE has been the lack of a good correlation between blood levels and the severity of HE.[20] At physiological pH, blood ammonia is mostly ionized (NH_4^+). Small changes in pH have effects in the equilibrium and affect the amount of un-ionized ammonia (NH_3), which is the form that passes the blood-brain barrier by diffusion. In some studies, the correlation between arterial ammonia and HE has been improved after adjusting for pH,[21] but this has not been confirmed by other authors.[22] Part of the lack of association between plasma ammonia and HE can be accounted for by differences in ammonia concentration between blood and the central nervous system. This difference could be explained by differences in pH between the compartments and by the presence of active transporters. It has been estimated that at least 20% of ammonia may pass the blood-brain barrier ionized (NH_4^+) through an active transport.[23] Cerebral blood flow and the permeability surface area are other elements that may determine the delivery of ammonia to the brain.[24]

Inflammation

Apart from ammonia, there are other factors that appear to have an important role in the development of HE. This is apparent from the differences between HE in cirrhosis and other diseases that share high levels of ammonia but different clinical outcomes, such as inborn errors of metabolism or congenital portal-systemic shunts.[25] In the latter, magnetic resonance studies and oral glutamine challenge tests have reproduced the same abnormalities as those present in cirrhosis.[26] However, episodic HE is very infrequent in patients with congenital shunts. One factor that may explain the development of episodic HE in cirrhosis is inflammation.[27] The presence of markers of a systemic inflammatory response has been linked to HE.[28] In patients with acute liver failure, it is well documented that the progression to severe HE is associated with infection.[29] The exposition of astrocytes to cytokines in cultures induces astrocyte swelling, which is considered a neuropathological hallmark of HE.[30] In experimental models, lipopolysaccharide enhances ammonia-induced changes in cerebral hemodynamics.[31] For these reasons, it has been postulated that the inflammatory response may unlock the blood-brain barrier to the effects of toxins and may be responsible for most of the bouts of overt HE.[32] Interestingly, subclinical infection has been demonstrated among patients with advanced cirrhosis.[33] The induction of inflammatory response by these infections may cause those episodes of HE in which a precipitating event cannot be identified.

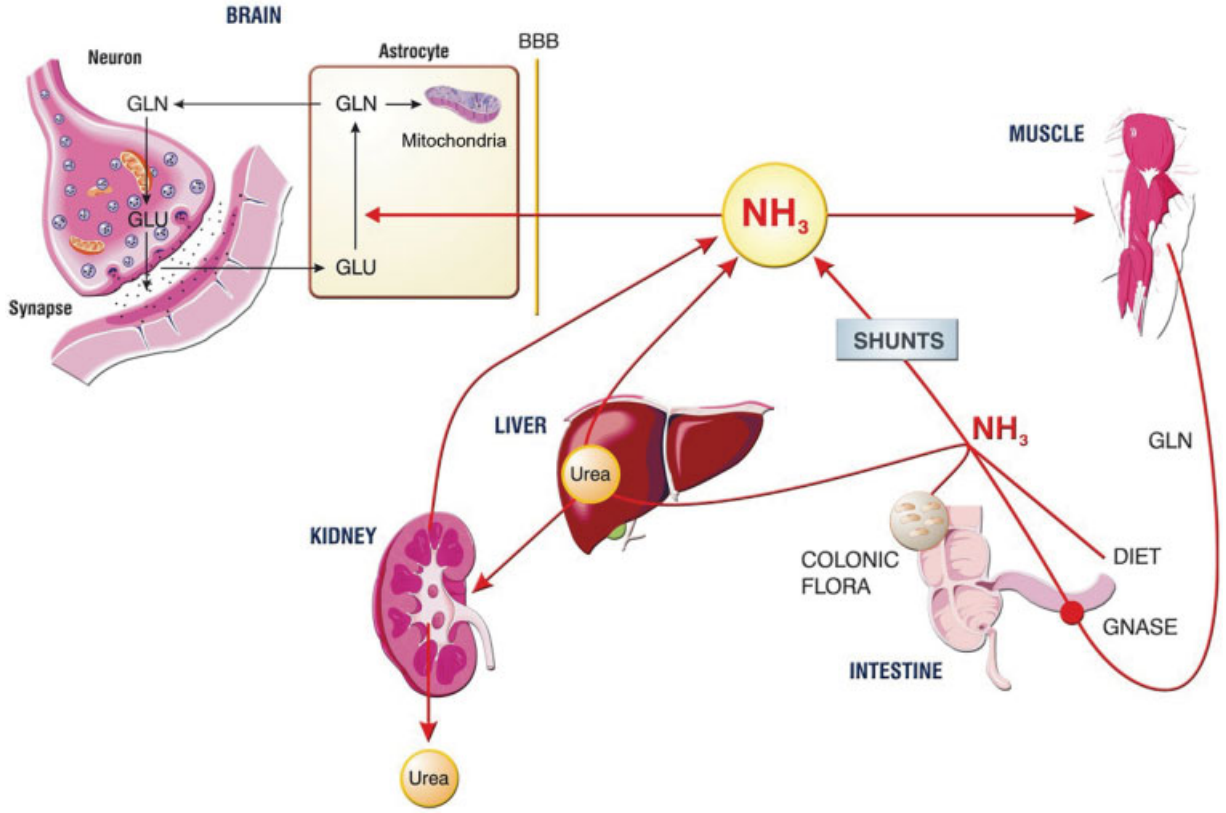

Figure 1 Interorgan ammonia trafficking and metabolism. Ammonia is generated in the intestines from nitrogenous compounds from the diet, deamination of glutamine by glutaminase, and metabolism of nitrogenous substances by colonic flora. In normal circumstances, most ammonia is metabolized to urea in the liver. Portal-systemic shunts and liver failure cause a rise in blood ammonia that may affect brain function by inducing several disturbances in astrocytes; these may impair mitochondria and the glutamate-glutamine trafficking between neurons and astrocytes. Skeletal muscle is capable of decreasing blood ammonia by metabolizing ammonia to glutamine. The kidney has also an important role in determining blood ammonia by excreting urea in the urine and generating ammonia. NH_3, ammonia; GLU, glutamate; GLN, glutamine; GNASE, glutaminase; BBB, blood-brain barrier.

Brain Disturbances

New technological advances have allowed a better knowledge of the disturbances present in the brain in HE, not only in experimental models, but also in patients with cirrhosis. Results of neuropathologic, spectroscopic, and neurochemical studies continue to indicate a major role for ammonia.[34] Although there is no unifying hypothesis, the molecular mechanisms of ammonia toxicity point at two important steps: (1) abnormalities in the metabolism of neurotransmitters and (2) neurotoxicity induced by oxidative stress.

Glutamate is an amino acid that acts as an excitatory neurotransmitter and is present in presynaptic vesicles in more than 90% of the neurons. After its release and activation of different postsynaptic receptors, glutamate is removed from the synaptic cleft by transporters located at the astrocytes. In the astrocytes, glutamate is transformed into glutamine with the incorporation of one molecule of ammonia and transported into the presynaptic neuron, where glutamine will be transformed again into glutamate. This cycle is affected at several steps by ammonia,[35] which has led to the proposal that impaired glutamatergic neurotransmission induces part of the neurological manifestations of HE.[36] However, experimental attempts to modify these abnormalities have shown only marginal amelioration.[37] Another neurotransmitter system that is affected by ammonia is the inhibitory GABAergic neurotransmission. One of the mechanisms involved is the activation of neurosteroids, which are agonists of the γ-aminobutyric acid (GABA) receptor and may be responsible for the inhibitory pattern of neuronal function that characterizes HE.[38]

Ammonia has been shown to evoke oxidative stress inducing the generation of free radicals and the nitrotyrosination of proteins in the brain.[39] This process is critical for mitochondrial function and secondarily may cause failure of normal neurotransmission. Signs of impending energy failure have been shown in experimental models[40] and in patients with acute liver

failure.[41] An additional effect of oxidative and nitrosative stress in astrocytes is the induction of swelling,[42] which has been consistently reproduced after exposure to ammonia.[43] Astrocyte swelling can be exacerbated by some of the factors that precipitate HE, such as inflammatory mediators, hyponatremia, and benzodiazepines.[44] The change in the state of cellular hydration causes impairment of several metabolic pathways and has been suggested as being responsible for brain edema and for the neurological manifestations of HE.[45]

CLINICAL ASSESSMENT

The complexity of the multiple functions of the brain explains the difficulties in assessing and monitoring HE, a disorder that causes a generalized disturbance of brain function. There are many systems of variable sophistication that have been proposed[46] to cover the whole spectrum of HE (electroencephalogram, evoked potentials). However, as highlighted in the Vienna conference,[1] simple tools that may be used at the bedside are preferable. One approach may be the combination of several simple neurological scales and neuropsychological test that are already available, depending on the severity of HE (Fig. 2).

Grading Episodic Hepatic Encephalopathy

Episodic HE is characterized by rapid fluctuations in the mental state. As in other metabolic encephalopathies, the confusional syndrome can be identified simply with the four questions of the Confusion Assessment Method.[47] A precise gradation of HE may help to detect the presence of new precipitating factors early on and proceed to their adequate treatment. The West Haven scale establishes four stages of HE according to alterations in the state of consciousness, intellectual function, behavior, and neuromuscular signs.[1] The scale includes multiple manifestations for each stage, but lacks specific definitions. In clinical practice, doctors do not check for the presence of all the manifestations and use the scale in an intuitive approach that has been authorized for its wide use. However, this makes grading of HE subjective, which does not invalidate the scale in individual cases, but may cause discrepancies between different observers and affect the results of multicenter trials. One method to improve the reliability of the West Haven scale is to use well-defined operational criteria and combine them with psychometric tests, as proposed by the Hepatic Encephalopathy Scaling Algorithm (HESA).[48] A simpler alternative that has been recently developed is the clinical hepatic encephalopathy staging scale (CHESS).[49] The CHESS is a linear scale that

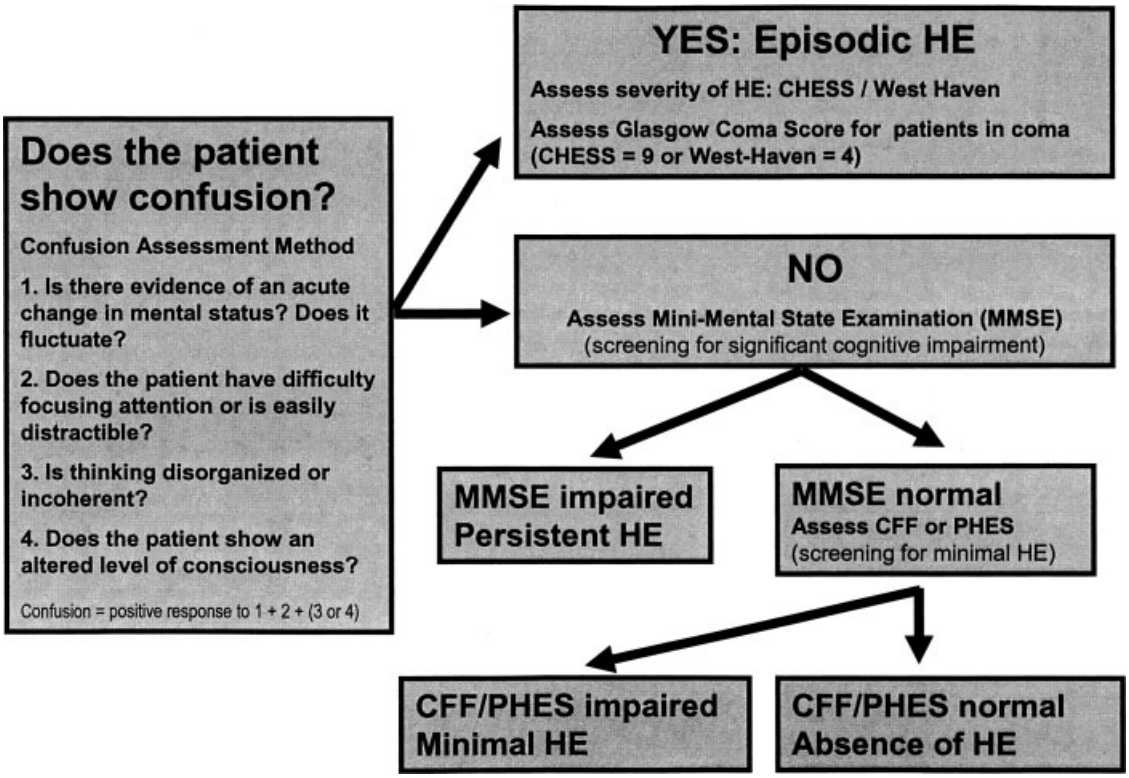

Figure 2 Algorithm for grading hepatic encephalopathy using simple clinical scales. The questions of the CAM (Confusion Assessment Method) have been abbreviated due to space constraints. HE, hepatic encephalopathy; CHESS, clinical hepatic encephalopathy staging scale; CFF, critical flicker frequency; PHES, psychometric hepatic encephalopathy score; MMSE, Mini-Mental State Examination.

Table 1 Clinical Hepatic Encephalopathy Staging Scale (CHESS)

Item	Score 0	Score 1
1. Does the patient know which month he/she is in (i.e., January, February)?	Yes	No, or he/she does not talk
2. Does the patient know which day of the week he/she is in (i.e., Thursday, Friday, Sunday, etc.)?	Yes	No, or he/she does not talk
3. Can he/she count backward from 10 to 1 without making mistakes or stopping?	Yes	No, or he/she does not talk
4. If asked to do so, does he/she raise his/her arms?	Yes	No
5. Does he/she understand what you are saying to him/her? (based on the answers to questions 1 to 4)	Yes	No, or he/she does not talk
6. Is the patient awake and alert?	Yes	No, he/she is sleepy or fast asleep
7. Is the patient fast asleep, and is it difficult to wake him/her up?	No	Yes
8. Can he/she talk?	Yes	He/she does not talk
9. Can he/she talk correctly? In other words, can you understand everything he/she says, and he/she doesn't stammer?	Yes	No, he/she does not talk or does not talk correctly
Total score of the CHESS:		

The total score is the sum of the answers to the nine items. Minimal score = 0; maximal score = 9.

scores HE from 0 (normal mental state) to 9 (deep coma) according to presence or absence of nine items (Table 1). Irrespective of the scale that is used, for patients in coma it is recommended to complete the assessment with the Glasgow Coma Score.[1]

Diagnosis of Minimal Hepatic Encephalopathy

The main reason to investigate the presence of minimal HE is to advise patients with cirrhosis who are at risk for accidents, such as active drivers, those with a decline in work performance, or those who complain of cognitive symptoms.[50] A complete psychometric assessment by a neuropsychologist is the best way to know to what extent the patient suffers a cognitive impairment and how it interferes with daily life. However, this evaluation is not easy to carry out due to its costs, complexity, and length. There are many diagnostic methods that have been proposed instead. Any technique that demonstrates abnormalities of the central nervous system attributable to liver failure in a patient with cirrhosis and a normal mental state on physical exam would be valid. Unfortunately, an arbitrary consensus to define a gold standard to compare the reliability of the different methods has not been reached. The current recommendation is to apply short diagnostic batteries of neuropsychological tests adapted to the cultural characteristics of the population being evaluated. One of these tests, which is being increasingly used in different countries, is the psychometric hepatic encephalopathy score (PHES).[51] One alternative is computerized tests, such as the critical flicker frequency (CFF).[52] The CFF consists of identifying the frequency at which a high-frequency flickering light, perceived as a continuous light at first, begins to be perceived intermittently once the frequency of flickering progressively decreases. Inattentive subjects that exhibit minimal or overt HE perceive the intermittency at a lower frequency. The value of the CFF is supported by the finding that cirrhotic patients with a CFF < 38 Hz are at higher risk for episodic HE.[53]

Imaging of the Portal-Systemic Circulation

The importance of portal-systemic shunting in inducing HE is well known from the experience with surgical shunts and transjugular intrahepatic portal-systemic shunt (TIPS).[54] This experience shows that there is a balance between the risk of HE and the risk of gastrointestinal bleeding.[55] Cirrhotic patients with persistent or recurrent HE commonly have large spontaneous portal-systemic shunts.[56] It is currently possible to obtain high-quality three-dimensional images of these vessels with helical computed tomography and magnetic resonance. These methods are especially valuable in the diagnosis of patients with neurological manifestations compatible with HE but with normal or only slightly abnormal liver tests.[57] The steal of portal flow caused by these large shunts is an important mechanism in the induction of HE.[58] Increasing portal flow with the occlusion of the shunts improves HE. This can be performed safely with angioradiological procedures,[59] but occlusion of shunts should be reserved for patients without large varices and relatively well-preserved liver function (normal bilirubin). On other occasions, imaging of the portal-systemic circulation may reveal portal vein thrombosis.[60] There is a current tendency to indicate anticoagulation in this situation, even if associated with cirrhosis.[61] From a theoretical point of view, it is

possible that the benefits of anticoagulation include a decrease in the development of HE.

Magnetic Resonance of the Brain

Magnetic resonance of the brain has become a standard technique for the assessment of patients with neurological manifestations. In patients with cirrhosis, magnetic resonance is useful to exclude alternative diagnoses to HE. In addition, there are a series of abnormalities found by various techniques that have been very useful for a better understanding of the pathogenesis of HE and are increasingly being applied in its diagnosis and monitoring.

Proton magnetic resonance imaging shows a typical pallidal hyperintensity on T1-weighted images in cirrhotic patients.[62] This probably indicates deposition of manganese,[63] which may intervene in the development of extrapyramidal manifestations. Pallidal hyperintensity is not related to the grade of HE,[64] but rather its absence in a patient with cirrhosis and neurological manifestations suggests an alternative diagnosis. Proton magnetic resonance spectroscopy allows the assessment of several brain metabolites (glutamine, glutamate, *myo*-inositol) that may participate in the pathogenesis of HE. The pattern of a decrease of *myo*-inositol and an increase of glutamine is characteristic of HE.[65] Severity of HE has been associated with the intensity of this abnormality.[66] However, neither cut-off values or the diagnostic accuracy of this pattern have been established.

Magnetization transfer and diffusion-weighted images are techniques sensitive to detect changes in the amount of water in different compartments of the brain. They have shown signs compatible with an increase in extracellular water in patients with cirrhosis and minimal or mild HE.[67–69] Several investigators are trying to establish systems to quantify changes in brain water and use them in the diagnosis and monitoring of HE. Meanwhile, these findings are intriguing in terms of pathogenesis, because they contradict the hypothesis that the increase in brain water is intracellular and secondary to astrocyte swelling.[70] An explanation for an increase in extracellular brain water could be impairment of the blood-brain barrier, as suggested by the evolution of focal white matter lesions after improving HE.[71] Cirrhotic patients with HE and white matter lesions, induced by small-vessel disease secondary to vascular risk factors, may exhibit large modifications in their volume due to changes in the amount of focal brain edema (Fig. 3).

TREATMENT

Reappraisal of Current Therapies

Since the finding that the administration of nitrogenous compounds could precipitate HE, the focus of therapy has been to reduce ammonia generated in the colon. Therefore, the mainstays of therapy have been the administration of antibiotics (neomycin, rifaximin, vancomycin), nonabsorbable disaccharides (lactulose, lactitol), and protein-restricted diets.[72] As discussed above, current knowledge indicates that organs other than the colon have an important role in determining blood ammonia concentration. From this perspective, the data on which the efficacy of current therapy was based have been reappraised.[73] A meta-analysis investigated the effect of nonabsorbable disaccharides (lactulose or lacitol) compared with placebo, antibiotics, or no intervention.[74] The main result is that nonabsorbable disaccharides seem to reduce the risk of no improvement of HE, but are inferior to antibiotics. However, the results were not homogeneous and the analysis of the two high-quality trials (44 patients) that compared nonabsorbable disaccharides to placebo found no significant effect. These data have generated a controversy of whether or not nonabsorbable disaccharides should be used. Most authors agree that the data on the biological effects of these compounds and a large clinical experience are sufficient to justify their use.[75] The meta-analysis reflects the difficulties in designing clinical trials for HE, where multiple confounding factors are hard to control, and indicates that future studies of new compounds should compare them against placebo. The use of antibiotics to treat HE was reinforced by the meta-analysis. Nevertheless, antibiotics have secondary effects that may be severe, especially if administered for long periods.[76]

Protein restriction has been strongly advocated for patients with HE.[77] The recommendation is so deeply present in clinical practice[78] that even societies of nutritionists have found difficulty in eliminating protein restriction from their guidelines until recently.[79] However, the basis for protein restriction has been anecdotal.[80] Protein restriction may be harmful as shown in an analysis of clinical trials in alcoholic liver disease that observed increased mortality among patients who received diets with a low amount of protein.[81] In patients with episodic HE, the only randomized trial that has been conducted did not find differences in the outcome of HE between a low and a normal protein diet.[13] Protein restriction favors protein degradation and if maintained for long periods worsens the nutritional status. While a high content of proteins in the diet induces hyperammonemia and may precipitate HE, the contrary may not be true.[82] Thus, protein restriction is no longer recommended.

Liver Transplantation

The development of HE in patients with cirrhosis is associated with a survival lower than 50% at 1 year.[83] For this reason, liver transplantation should be considered in these patients.[84] Many countries have adopted the model

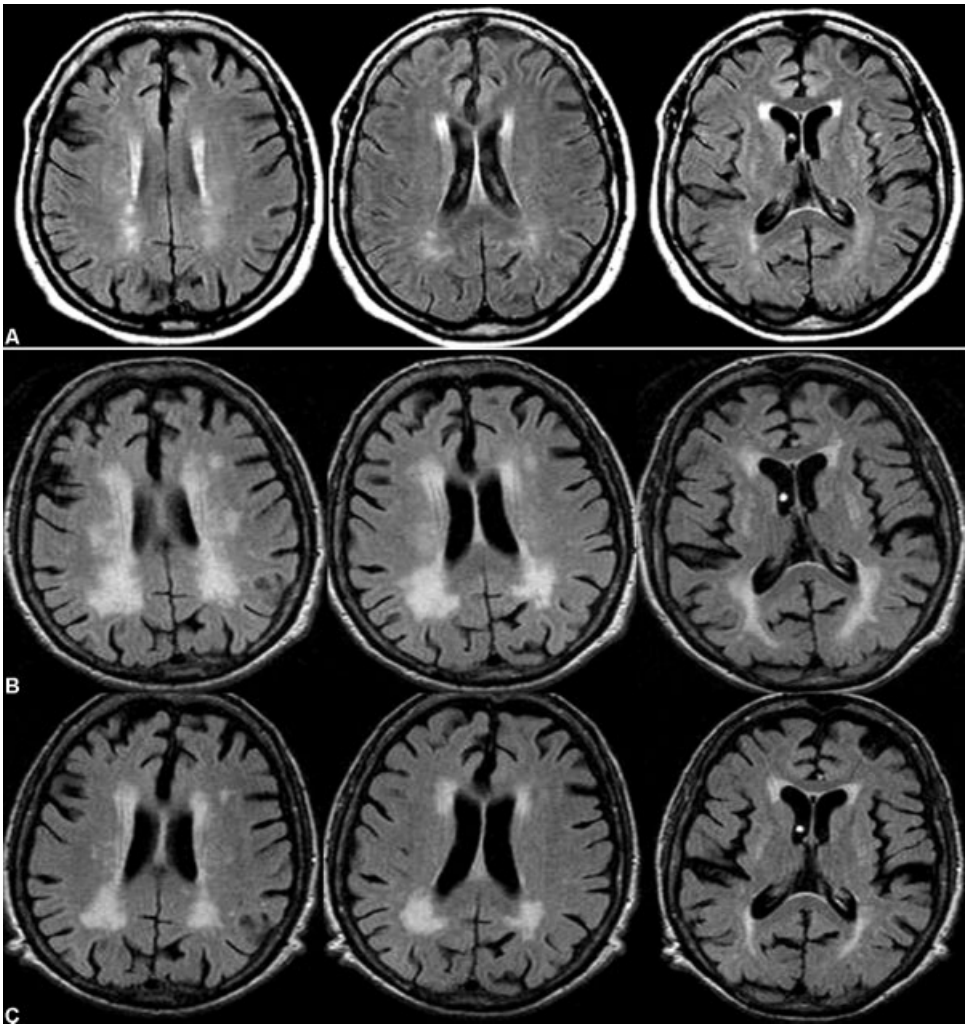

Figure 3 Magnetic resonance imaging of the brain using fluid attenuation inversion recovery (FLAIR) in a female patient with insulin-dependent diabetes mellitus and cryptogenic cirrhosis (probably secondary to nonalcoholic steatohepatitis) that was diagnosed as HE in 1999, when she was 52 years old, using magnetic resonance. (A) The first magnetic resonance imaging, performed while she exhibited minimal HE, showed an increase of the signal along the corticospinal tract. During the following years, the patient experienced several bouts of HE and mild chronic manifestations (slurred speech, mild cognitive impairment). (B) Magnetic resonance performed 8 years later during an episode of HE grade 3 showed diffuse periventricular white matter lesions. (C) One month later, when HE was grade 1, white matter lesions were markedly reduced. (Data from Mínguez B, Rovira A, Alonso J, et al. Decrease in the volume of white matter lesions with improvement of hepatic encephalopathy. AJNR Am J Neuroradiol 2007;28:1499–1500.)

for end-stage liver disease (MELD) system to prioritize the allocation of organs to those recipients with worse prognoses. The MELD has many advantages, but one limitation is that it may underestimate the prognosis of patients that had developed HE.[85] To the contrary, there is a subgroup of patients who exhibit recurrent HE associated with large spontaneous portal-systemic shunts and relatively preserved liver function (that is, normal bilirubin) who exhibit a better survival.[56]

Liver transplantation improves HE, even in patients with severe manifestations.[86,87] One difficulty in assessing liver transplant candidates with cognitive deterioration is to distinguish those with persistent HE from other causes (for example, vascular cognitive impairment, incipient Alzheimer's disease). This is complicated by the observation that focal white matter lesions secondary to small-vessel cerebral disease markedly decrease in their volume after liver transplantation.[71] Thus, the presence of these lesions (even if extensive as in Fig. 3) does not imply that the cognitive impairment is of vascular origin. Similarly, mild to moderate brain atrophy is found in the majority of patients with persistent HE[88] and does not necessarily indicate progressive dementia. In patients with the prior findings in magnetic resonance imaging, our practice is to attribute neurological manifestations to HE if they have a fluctuating course and if magnetic resonance spectroscopy of the brain shows high levels of glutamine and normal or only

slightly decreased levels of n-acetyl-aspartate (a marker of neuronal loss).

Prospective studies that have assessed neuropsychological function following liver transplantation have challenged the notion of complete reversibility of HE.[89] It is possible that HE causes some irreversible sequelae.[90] However, there are multiple factors that may affect cognitive function following liver transplantation.[91] Neurological complications are frequent, especially in the postoperative period.[92] Special care should be taken to avoid neurotoxicity of immunosuppressors and to treat vascular risk factors, such as diabetes mellitus and arterial hypertension, that are common following liver transplantation. Patients who have experienced HE prior to liver transplantation are more sensitive to developing neurological complications. The diagnosis of changes in mental state following liver transplantation is challenging. A simple model of four preoperative predictors (alcoholic or metabolic etiology, MELD >15, mechanical ventilation, nonelective transplantation) has been proposed to identify those patients at a higher risk for neurological complications.[93]

Future Prospects

There are three main focuses of research that may benefit patients with HE: drugs that decrease plasma ammonia, measures to reduce brain edema, and liver-support devices. Theoretically, the generation of ammonia in the small intestine may be reduced by inhibiting glutaminase.[5] However, since glutamine is a major energetic substrate of the intestine this may result in serious adverse effects.[94] An alternative mechanism to decrease ammonia is to increase the disposal by stimulating the synthesis of nontoxic nitrogenous compounds. Muscle may become an important organ to enhance ammonia detoxification by conversion to glutamine. L-ornithine-L-aspartate, which has undergone clinical evaluation[95] and is available in several countries, and L-ornithine phenylacetate, a recent proposal,[96] provide intermediates for glutamine synthesis and decrease plasma ammonia.

Hyponatremia, a common disturbance in patients with advanced cirrhosis and ascites, enhances brain edema.[97,98] Increasing plasma osmolality improves the management of brain edema in fulminant hepatic failure.[99] In cirrhosis, this can be achieved with aquaretic drugs[100] that, through this mechanism, may decrease the incidence of HE. Specifically targeted anti-inflammatory drugs do not seem to become a realistic approach in the near future because there are multiple mediators that may precipitate HE.[28] Probiotic therapy, which has been shown to improve minimal HE,[101] modifies intestinal flora, decreases plasma ammonia, may diminish bacterial translocation,[102] and might reduce the induction of inflammatory mediators. Liver-support devices, such as the molecular adsorbents recirculating system (MARS) might also play a role. MARS improves the grade of HE[103] independently of changes in ammonia and cytokines, suggesting that other toxins, such as oxygen-based free radicals, might be important.

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ABBREVIATIONS

CFF	critical flicker frequency
CHESS	clinical hepatic encephalopathy staging scale
GABA	γ-aminobutyric acid
HE	hepatic encephalopathy
HESA	hepatic encephalopathy scaling algorithm
MARS	molecular adsorbents recirculating system
MELD	model for end-stage liver disease
MMSE	mini-mental state examination
PHES	psychometric hepatic encephalopathy score
TIPS	transjugular intrahepatic portosystemic shunt

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;35:716–721
2. Conn HO. Portal-systemic shunting and portal-systemic encephalopathy: a predictable relationship. Hepatology 1995; 22:365–367
3. Shawcross DL, Damink SW, Butterworth RF, Jalan R. Ammonia and hepatic encephalopathy: the more things change, the more they remain the same. Metab Brain Dis 2005;20:169–179
4. Huizenga JR, Gips CH, Tangerman A. The contribution of various organs to ammonia formation: a review of factors determining the arterial ammonia concentration. Ann Clin Biochem 1996;33:23–30
5. Romero-Gomez M. Role of phosphate-activated glutaminase in the pathogenesis of hepatic encephalopathy. Metab Brain Dis 2005;20:319–325
6. Romero-Gomez M, Ramos-Guerrero R, Grande L, et al. Intestinal glutaminase activity is increased in liver cirrhosis and correlates with minimal hepatic encephalopathy. J Hepatol 2004;41:49–54
7. Hawkins RA, Jessy J, Mans AM, Chedid A, DeJoseph MR. Neomycin reduces the intestinal production of ammonia from glutamine. Adv Exp Med Biol 1994;368:125–134
8. Albrecht J, Norenberg MD. Glutamine: a Trojan horse in ammonia neurotoxicity. Hepatology 2006;44:788–794
9. Olde Damink SW, Jalan R, Redhead DN, Hayes PC, Deutz NE, Soeters PB. Interorgan ammonia and amino acid metabolism in metabolically stable patients with cirrhosis and a TIPSS. Hepatology 2002;36:1163–1171

10. Kondrup J, Nielsen K, Juul A. Effect of long-term refeeding on protein metabolism in patients with cirrhosis of the liver. Br J Nutr 1997;77:197–212
11. Olde Damink SW, Jalan R, Deutz NE, et al. Isoleucine infusion during "simulated" upper gastrointestinal bleeding improves liver and muscle protein synthesis in cirrhotic patients. Hepatology 2007;45:560–568
12. Mendenhall CL, Moritz TE, Roselle GA, et al. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. The VA Cooperative Study Group #275. JPEN J Parenter Enteral Nutr 1995;19:258–265
13. Córdoba J, López-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41:38–43
14. Plauth M, Merli M, Weimann A, Ferenci P, Mueller MJ. ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr 1997;16:43–55
15. Moriwaki H, Miwa Y, Tajika M, Kato M, Fukushima H, Shiraki M. Branched-chain amino acids as a protein- and energy-source in liver cirrhosis. Biochem Biophys Res Commun 2004;313:405–409
16. Marchesini G, Bianchi G, Merli M, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind randomized trial. Gastroenterology 2003;124:1792–1801
17. Marchesini G, Dioguardi FS, Bianchi GP, et al. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy: a randomized double-blind casein-controlled trial. J Hepatol 1990;11:92–101
18. Olde Damink SWM, Jalan R, Deutz NE, et al. The kidney plays a major role in the hyperammonemia seen after simulated or actual GI bleeding in patients with cirrhosis. Hepatology 2003;37:1277–1285
19. Jalan R, Kapoor D. Enhanced renal ammonia excretion following volume expansion in patients with well compensated cirrhosis of the liver. Gut 2003;52:1041–1045
20. Lockwood AH. Blood ammonia levels and hepatic encephalopathy. Metab Brain Dis 2004;19(3–4):345–349
21. Kramer L, Tribl B, Gendo A, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology 2000;31:30–34
22. Nicolao F, Efrati C, Masini A, Merli M, Attili AF, Riggio O. Role of determination of partial pressure of ammonia in cirrhotic patients with and without hepatic encephalopathy. J Hepatol 2003;38:441–446
23. Ott P, Larsen FS. Blood-brain barrier permeability to ammonia in liver failure: a critical reappraisal. Neurochem Int 2004;44:185–198
24. 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; 11:337–341
25. Watanabe A. Portal-systemic encephalopathy in non-cirrhotic patients: classification of clinical types, diagnosis and treatment. J Gastroenterol Hepatol 2000;15:969–979
26. Ortiz M, Córdoba J, Alonso J, et al. Oral glutamine challenge and magnetic resonance spectroscopy in three patients with congenital portosystemic shunts. J Hepatol 2004;40:552–557
27. Blei AT. Infection, inflammation and hepatic encephalopathy, synergism redefined. J Hepatol 2004;40:327–330
28. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology 2000;32:734–739
29. Vaquero J, Polson J, Chung C, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology 2003;125:755–764
30. Häussinger D, Schliess F. Astrocyte swelling and protein tyrosine nitration in hepatic encephalopathy. Neurochem Int 2005;47;(1–2):64–70
31. Pedersen HR, Ring-Larsen H, Olsen NV, Larsen FS. Hyperammonemia acts synergistically with lipopolysaccharide in inducing changes in cerebral hemodynamics in rats anaesthetised with pentobarbital. J Hepatol 2007;47:245–252
32. Jalan R, Bernuau J. Induction of cerebral hyperemia by ammonia plus endotoxin: does hyperammonemia unlock the blood-brain barrier? J Hepatol 2007;47:168–171
33. Such J, Frances R, Munoz C, et al. Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, nonneutrocytic ascites. Hepatology 2002;36:135–141
34. Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at ammonia. Metab Brain Dis 2002;17: 221–227
35. Norenberg MD. Astrocytic-ammonia interactions in hepatic encephalopathy. Semin Liver Dis 1996;16:245–253
36. Butterworth RF. Hepatic encephalopathy and brain edema in acute hepatic failure: does glutamate play a role? Hepatology 1997;25:1032–1033
37. Vogels BA, Maas MA, Daalhuisein J, Quack G, Chamuleau RA. Memantine, a non-competitive NMDA receptor antagonist improves hyperammonemia-induced encephalopathy and acute hepatic encephalopathy in rats. Hepatology 1997;25:820–827
38. Ahboucha S, Layrargues GP, Mamer O, Butterworth RF. Increased brain concentrations of a neuroinhibitory steroid in human hepatic encephalopathy. Ann Neurol 2005;58: 169–170
39. Norenberg MD. Oxidative and nitrosative stress in ammonia neurotoxicity. Hepatology 2003;37:245–248
40. Chatauret N, Zwingmann C, Rose C, Leibfritz D, Butterworth RF. Effects of hypothermia on brain glucose metabolism in acute liver failure: a H/C-nuclear magnetic resonance study. Gastroenterology 2003;125:815–824
41. Wendon JA, Harrison PM, Keays R, Williams R. Cerebral blood flow and metabolism in fulminant liver failure. Hepatology 1994;19:1407–1413
42. Schliess F, Gorg B, Häussinger D. Pathogenetic interplay between osmotic and oxidative stress: the hepatic encephalopathy paradigm. Biol Chem 2006;387(10–11):1363–1370
43. Norenberg MD, Baker L, Norenberg LO. Ammonia-induced astrocyte swelling in primary cultures. Neurochem Res 1991;16:833–836
44. Gorg B, Foster N, Reinehr R, et al. Benzodiazepine-induced protein tyrosine nitration in rat astrocytes. Hepatology 2003;37:334–342
45. Häussinger D, Kircheis G, Fischer R, Schliess F, vom Dahl S. Hepatic encephalopathy in chronic liver disease: a clinical manifestation of astrocyte swelling and low-grade cerebral edema? J Hepatol 2000;32:1035–1038
46. Amodio P, Gatta A. Neurophysiological investigation of hepatic encephalopathy. Metab Brain Dis 2005;20:369–379

47. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion—the confusion assessment method: a new method for detection of delirium. Ann Intern Med 1990;113:941–948
48. Hassanein TI, Hilsabeck RC, Perry W. Introduction to the Hepatic Encephalopathy Scoring Algorithm (HESA). Dig Dis Sci 2008;53:529–538
49. Ortiz M, Córdoba J, Doval E, et al. Development of a clinical hepatic encephalopathy staging scale. Aliment Pharmacol Ther 2007;26:859–867
50. Ortiz M, Jacas C, Córdoba J. Minimal hepatic encephalopathy: diagnosis, clinical significance and recommendations. J Hepatol 2005;42(suppl 1):S45–S53
51. Weissenborn K, Ennen JC, Rückert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34:768–773
52. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Häussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. Hepatology 2002;35: 357–366
53. Romero-Gomez M, Córdoba J, Jover R, et al. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatology 2007;45:879–885
54. Hassoun Z, Deschenes M, Lafortune M, et al. Relationship between pre-TIPS liver perfusion by the portal vein and the incidence of post-TIPS chronic hepatic encephalopathy. Am J Gastroenterol 2001;96:1205–1209
55. Blei AT. Hepatic encephalopathy in the age of TIPS. Hepatology 1994;20(1 Pt 1):249–252
56. Riggio O, Efrati C, Catalano C, et al. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case-control study. Hepatology 2005;42: 1158–1165
57. Córdoba J, Hinojosa C, Sampedro F, et al. Usefulness of magnetic resonance spectroscopy for diagnosis of hepatic encephalopathy in a patient with relapsing confusional syndrome. Dig Dis Sci 2001;46:2451–2455
58. Ohnishi K, Saito M, Sato S, et al. Direction of splenic venous flow assessed by pulsed Doppler flowmetry in patients with a large splenorenal shunt: relation to spontaneous hepatic encephalopathy. Gastroenterology 1985;89:180–185
59. Uflacker R, Silva A, d'Albuquerque LA, Piske RL, Mourao GS. Chronic portosystemic encephalopathy: embolization of portosystemic shunts. Radiology 1987;165:721–725
60. Mínguez B, Garcia-Pagan JC, Bosch J, et al. Noncirrhotic portal vein thrombosis exhibits neuropsychological and MR changes consistent with minimal hepatic encephalopathy. Hepatology 2006;43:707–714
61. Francoz C, Belghiti J, Vilgrain V, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut 2005;54:691–697
62. Kulisevsky J, Pujol J, Balanzo J, et al. Pallidal hyperintensity on magnetic resonance imaging in cirrhotic patients: clinical correlations. Hepatology 1992;16:1382–1388
63. Rose C, Butterworth RF, Zayed J, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. Gastroenterology 1999;117:640–644
64. Spahr L, Butterworth RF, Fontaine S, et al. Increased blood manganese in cirrhotic patients: relationship to pallidal magnetic resonance signal hyperintensity and neurological symptoms. Hepatology 1996;24:1116–1120
65. Kreis R, Ross BD, Farrow NA, Ackerman Z. Metabolic disorders of the brain in chronic hepatic encephalopathy detected with H-1 MR spectroscopy. Radiology 1992;182: 19–27
66. Lee JH, Seo DW, Lee Y-S, et al. Proton magnetic resonance spectroscopy (1H-MRS) findings for the brain in patients with liver cirrhosis reflect the hepatic functional reserve. Am J Gastroenterol 1999;94:2206–2213
67. Córdoba J, Alonso J, Rovira A, Jacas C, Sanpedro F, Castells LL, 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
68. Lodi R, Tonon C, Stracciari A, et al. Diffusion MRI shows increased water apparent diffusion coefficient in the brains of cirrhotics. Neurology 2004;62:762–766
69. Kale RA, Gupta RK, Saraswat VA, et al. Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. Hepatology 2006;43:698–706
70. Córdoba J, Blei AT. Brain edema and hepatic encephalopathy. Semin Liver Dis 1996;16:271–280
71. Rovira A, Mínguez B, Aymerich FX, et al. Decreased white matter lesion volume and improved cognitive function after liver transplantation. Hepatology 2007;46:1485–1490
72. Córdoba J, Blei AT. Treatment of hepatic encephalopathy. Am J Gastroenterol 1997;92:1429–1439
73. Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. Lancet 2005;365:431–433
74. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004;328:1046
75. Blei AT. Treatment of hepatic encephalopathy. Lancet 2005;365:1383–1384
76. Curioso WH, Monkemuller KE. Neomycin should not be used to treat hepatic encephalopathy. BMJ 2001;323:233
77. Riordan SM, Williams R. Treatment of hepatic encephalopathy. N Engl J Med 1997;337:473–479
78. Soulsby CT, Morgan MY. Dietary management of hepatic encephalopathy in cirrhotic patients: survey of current practice in United Kingdom. BMJ 1999;318:1391
79. Plauth M, Cabre E, Riggio O, et al. ESPEN guidelines on enteral nutrition: liver disease. Clin Nutr 2006;25:285–294
80. Mullen KD, Weber FL Jr. Role of nutrition in hepatic encephalopathy. Semin Liver Dis 1991;11:292–304
81. Kondrup J, Muller MJ. Energy and protein requirements of patients with chronic liver disease. J Hepatol 1997;27:239–247
82. Felipo V, Miñana D, Grisolia S. Control of urea synthesis and ammonia utilization in protein deprivation and refeeding. Arch Biochem Biophys 1991;285:351–356
83. Bustamante J, Rimola A, Ventura P, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol 1999;30:890–895
84. Murray KF, Carithers RL Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. Hepatology 2005;41:1407–1432
85. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. Liver Transpl 2007;13:1366–1371
86. Weissenborn K, Tietge UJ, Bokemeyer M, et al. Liver transplantation improves hepatic myelopathy: evidence by three cases. Gastroenterology 2003;124:346–351

87. Larsen FS, Ranek L, Hansen BA, Kirkegaard P. Chronic portosystemic hepatic encephalopathy refractory to medical treatment successfully reversed by liver transplantation. Transpl Int 1995;8:246–247
88. Zeneroli ML, Cioni G, Crisi G, Vezzelli C, Ventura E. Globus pallidus alterations and brain atrophy in liver cirrhosis patients with encephalopathy: an MR imaging study. Magn Reson Imaging 1991;9:295–302
89. Mechtcheriakov S, Graziadei IW, Mattedi M, et al. Incomplete improvement of visuo-motor deficits in patients with minimal hepatic encephalopathy after liver transplantation. Liver Transpl 2004;10:77–83
90. Rose C, Jalan R. Is minimal hepatic encephalopathy completely reversible following liver transplantation? Liver Transpl 2004;10:84–87
91. Amodio P, Biancardi A, Montagnese S, et al. Neurological complications after orthotopic liver transplantation. Dig Liver Dis 2007;39:740–747
92. Pujol A, Graus F, Rimola A, et al. Predictive factors of in-hospital CNS complications following liver transplantation. Neurology 1994;44:1226–1230
93. Kanwal F, Chen D, Ting L, et al. A model to predict the development of mental status changes of unclear cause after liver transplantation. Liver Transpl 2003;9:1312–1319
94. Plauth M, Raible A, Vieillard-Baron D, Bauder-Gross D, Hartmann F. Is glutamine essential for the maintenance of intestinal function? A study in the isolated perfused rat small intestine. Int J Colorectal Dis 1999;14:86–94
95. Kircheis G, Nilius R, Held C, 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;25:1351–1360
96. Jalan R, Wright G, Davies NA, Hodges SJ. L-ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy. Med Hypotheses 2007;69:1064–1069
97. Córdoba J, Gottstein J, Blei AT. Chronic hyponatremia exacerbates ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol 1998;29:589–594
98. Restuccia T, Gomez-Anson B, Guevara M, et al. Effects of dilutional hyponatremia on brain organic osmolytes and water content in patients with cirrhosis. Hepatology 2004;39:1613–1622
99. Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology 2004;39:464–470
100. Ginès P, Jimenez W. Aquaretic agents: a new potential treatment of dilutional hyponatremia in cirrhosis. J Hepatol 1996;24:506–512
101. 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;39:1441–1449
102. Chiva M, Soriano G, Rochat I, et al. Effect of lactobacillus johnsonii La1 and antioxidants on intestinal flora and bacterial translocation in rats with experimental cirrhosis. J Hepatol 2002;37:456–462
103. Hassanein TI, Tofteng F, Brown RS Jr, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology 2007;46:1853–1862