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Hepatic encephalopathy and its pathogenesis

Hepatic encephalopathy (HE) is defined as a potentially reversible disturbance in the function of central nervous system secondary to hepatic insufficiency or portal systemic shunting. This definition reflects a broad spectrum of neuropsychiatric manifestations, ranging from subtle alterations in neuropsychological tests to appearance of deep coma, brain edema and intracranial hypertension.[1]

Classification

The nomenclature of HE has been a reason for great confusion among the physicians. Recently, HE has been classified into groups and subgroups taking into account both the type of hepatic abnormality and the duration/characteristics of the symptoms. The classification of HE is discussed below:[2]

Type A. Encephalopathy associated with acute liver failure (type A, for acute).

Type B. Encephalopathy associated with portal–systemic bypass and no intrinsic hepatocellular disease (type B, for by-pass).

Type C. Encephalopathy associated with cirrhosis and portal hypertension and/or portal–systemic shunts (type C, for cirrhosis). Type C is further divided into:

C.1. *Episodic HE:* Subdivided into precipitated and spontaneous types, depending on the presence of precipitating factors. The occurrence of at least two episodes of episodic HE within one year is referred to as "recurrent encephalopathy".

C.2. *Persistent HE*: Includes cognitive deficits that impact negatively on social and occupational functioning, and is subdivided into mild and severe forms. Treatment-dependent persistent HE is a subgroup in which overt symptoms develop promptly after discontinuing medication.

C.3. *Minimal HE*: Refers to abnormalities of cognition, affection/emotion, behavior or bioregulation that are not usually detected by regular clinical examination; diagnosis of the same requires specific neuropsychological and neurophysiological tests.

The most valuable tools in the diagnosis of HE are clinical history and physical examination

Staging

The most valuable tools in the diagnosis of HE are clinical history and physical examination. Two staging criteria based on the clinical findings are used to assess

TABLE 1. Level of consciousness with the Glasgow coma scale (scores vary between 3–15 from unconsciousness to fully conscious state)

Eyes open		Best motor response		Best verbal response	
Spontaneously	4	Obeys verbal orders	6	Oriented, conversant	5
To command	3	Localizes painful stimuli	5	Disoriented, conversant	4
To pain	2	Painful stimulus, flexion	3	Inappropriate words	3
No response	1	Painful stimulus, extension	2	Inappropriate sounds	2
		No response	1	No response	1

the patients of HE. These criteria include the *West Haven criteria* and the *Glasgow coma scale.*

The *West Haven criteria* groups HE in four stages:[1,2]

Stage 0 shows lack of detectable changes in personality or behavior. Asterixis is absent in this stage.

Stage 1 includes trivial lack of awareness, euphoria, depression, anxiety, shortened attention span, impaired addition or subtraction, hypersomnia, insomnia, or inversion of sleep pattern. Asterixis can be detected at this stage.

HE is often precipitated by identifiable precipitating factors. Correction of these precipitating factors constitute a very important aspect of management of an episode of HE

Stage 2 includes lethargy or apathy, disorientation, inappropriate behavior, slurred speech and obvious asterixis is seen.

Stage 3 includes gross disorientation, bizarre behavior, semistupor to stupor, mild response to noxious stimuli. Asterixis is generally absent in these cases.

Stage 4 is coma and no response to noxious stimuli.

The Glasgow coma scale evaluates the level of consciousness in patients of acute and chronic liver disease. It measures the response to eye opening, verbal behavior and motor responsiveness and quantifies neurologic impairment in a continuous numerical scale (Table 1).[2] It is mainly useful for evaluation of advanced stages of HE.

Precipitating factors

HE is often precipitated by identifiable precipitating factors. These include gastrointestinal bleeding, infections, constipation, oral protein load, renal and electrolyte disturbances such as renal failure, metabolic alkalosis/acidosis, hypokalemia, dehydration and diuretic effects, and psychoactive medications such as benzodiazepines, narcotics and other sedatives (Table 2). It is also common following transjugular intrahepatic portal-systemic shunts (TIPS).[1–3] Correction of these precipitating factors constitute a very important aspect of management of an episode of HE.

Pathogenesis

The cause of HE is explained by a multifactorial theory wherein encephalopathy is thought to be induced by a variety of coma-inducing substances which are either reabsorbed from the gut or are products of the body's metabolism.[4] These include lowering of ammonia, fatty acids and mercaptone and other aggravating factors such as electrolyte imbalance.[5] Normally, these substances are effectively eliminated by the liver but in cases of liver disease hepatic detoxification is significantly impaired because of a decreased number of functional hepatocytes or the presence of portocaval collaterals.[4] Increased brain exposure to these substances leads to a distur-

TABLE 2. Common precipitating factors of hepatic encephalopathy

Increased nitrogen load	Drugs
Gastrointestinal bleeding	Narcotics, tranquilizers, sedatives
Excess dietary protein	
Azotemia	Miscellaneous
Constipation	Infection
	Surgery
Electrolyte imbalance	Superimposed acute liver disease
Hyponatremia	Progressive liver disease
Hypokalemia, metabolic alkalosis/acidosis	Transjugular intrahepatic portal-systemic
Hypoxia	shunt (TIPS)
Hypovolemia	

bance of normal neurotransmission and results in the clinical symptoms that are characteristic of HE.[2]

In addition, a number of other possible mechanisms have recently been proposed, including production of false neurotransmitters, activation of central gama aminobutyric acid-benzodiazepine receptors (GABA-BZ) by ligands of endogenous origin and altered cerebral metabolism. The various hypotheses of the pathogenesis of HE are not mutually exclusive.[5] It seems likely that many of the described abnormalities may present at the same time and may ultimately lead to development of HE although ammonia has been viewed as the most important factor in the genesis of HE.

Role of ammonia

Since the description of ammonia in the pathogenesis of HE over 100 years ago, more than 1200 papers have explored its role and confirmed that ammonia holds the key among all the agents thought to be responsible for encephalopathy.[6] The synergistic action of ammonia with other toxins may account for many of the abnormalities occurring in liver failure, such as the changes in blood-to brain transport of neurotransmitter precursors, the metabolism of amino acid neurotransmitters, and cerebral glucose oxidation. These changes further cause a shift in the balance between inhibitory and excitatory neurotransmission towards a net increase of inhibitory neurotransmission as a consequence of down-regulation of glutamate receptors and an increase in inhibitory neurotransmission by gama-aminobutyric acid.[7]

Ammonia metabolism

Ammonia production

While ammonia production occurs at several sites in the body, the chief source is the amino acid metabolism. Protein ingested from food flows into the bloodstream as amino acid and is stored in the free amino acid pool. The metabolism of amino acids leads to the production of glutamate which is converted to α-ketoglutarate and ammonia by glutamate dehydrogenase. Ammonia is also produced in the intestinal wall by the degradation of glutamine in the presence of glutaminase and emitted into the portal vein. Renal tubular cells of the kidneys form another site of ammonia production where the action of glutaminase on glutamine yields ammonia and part of which is absorbed into the renal vein. In blood, while most of the urea is excreted into urine, about 20–25% is degraded to ammonia by urease.

Ammonia catabolism

Although ammonia is constantly produced in the tissues, it is present in very low levels in blood. This is due to rapid removal of ammonia from the blood by the liver and the fact that many tissues, particularly muscles, release amino acid

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nitrogen in the form of glutamine and alanine rather than as free ammonia.

In liver (urea cycle)

The formation of urea through the urea cycle in liver (Fig. 1)[5] is the most important route for ammonia catabolism. The long-term regulation of urea cycle is carried out by the levels of transcription of enzymes. In cases of acute change in nitrogen loads by ingested food in the short-term, the activation of carbamyl phosphate synthetase stimulates the urea cycle. Urea travels in blood from liver to the kidneys where it passess into the glomerular filterate. A portion of urea synthesized in the liver diffuses from the blood into the intestine and is cleaved to CO_2 and ammonia. This ammonia is partly reabsorbed into the blood. In patients with liver disease ammonia is not detoxified in the liver and hence its concenteration rises (hyperammonemia) in the systemic circulation leading to CNS dysfunction.

In skeletal muscles (glutamine synthesis)

Recently significant role of the underlying mechanism of ammonia detoxication in muscle tissue has been elucidated.[5] The process of deamination of branched chain amino acids (BCAAs) conjugates with the conversion of α-ketoglutarate to glutamate in muscle tissue, which is further converted to glutamine by consuming ammonia. This reaction is catalyzed by the astrocytic enzyme glutamine synthetase.[2] In healthy subjects, about 50% of arterial ammonia is disposed off by skeletal muscle and this system seems to be augmented in cases of liver cirrhosis.[5]

The formation of urea through the urea cycle in liver is the most important route for ammonia catabolism

In brain

An increase in brain glutamine has been found to be a consistent finding in patients and experimental models of HE. Because glutamine is an organic osmolyte, its accumulation may play a major role in swelling of astrocytes which are the sole cells responsible for detoxification of ammonia in brain.[2] It is important to note that normal neurotransmission is highly dependent on adequate astrocytic function, and astrocytic alterations are associated with disturbed neurotransmission leading to changes of HE.

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Management of hepatic encephalopathy: Changing Perspectives

Identification followed by rigorous treatment of the precipitating factors is the most important consideration in the therapy of hepatic encephalopathy (HE). In addition, treatment of HE involves measures to lower ammonia levels in blood, medications to counteract effects of ammonia on brain cell function, devices to compensate for liver dysfunction and liver transplantation.[1] Multiple therapeutic modalities such as protein restriction, use of antibiotics, intestinal cleansing, lactulose, branched chain amino acids (BCAA) and ornithine aspartate (OA) have been proven to be effective in management of HE.[2] Among these approaches, evidence for proven therapeutic efficacy in HE on the basis of placebo-controlled trials exists for transplantation, protein restriction, administration of vegetable proteins, ornithine aspartate and oral BCAA and lactulose enemas. The efficacy of oral lactulose has not been demonstrated on the basis of placebo-controlled trials.[3] Management modalities can be grouped into the following:

1. **Nutritional management**
   During the last decade there is a growing recognition of the importance of dietary manipulations in diseases of gastroenterology. Concepts are changing and current evidence seems to contradict the older beliefs and suggests that neither low-fat diet in gall bladder disease nor protein restriction in HE should be used routinely in clinical practice.[4]

2. **Lowering nitrogenous load**
   Lowering of nitrogenous load is achieved either by administration of drugs that decrease intestinal generation of ammonia or by use of agents such as OA that enhance the metabolism of ammonia.[5]

3. **Drugs that affect neurotransmission**
   Flumazenil and bromocriptine administration may have a therapeutic role in selected patients of HE but are not recommended presently because of lack of evidence-based data supporting the use of these drugs.[5]

4. **Manipulation of the splanchnic circulation**
   The presence of large spontaneous portal systemic shunts should be sought in selected patients with recurrent episodes of HE despite medical therapy, where a precipitating factor is not found. Occlusion of portal systemic collaterals should be undertaken only in centers with experienced interventional radiologists and after all other medical measures have failed.[5]

At present dietary approach and lowering of nitrogenous load appear to be the most effective and established strategies in the management of HE. These are discussed in detail below.

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Dietary approach

Diet is very important in long-term maintenance of well-compensated chronic liver disease. Liver function can be influenced by dietary manipulation as ingested nutrients are mainly metabolized in the liver. Studies have shown that adequate energy intake needs to be maintained as a priority in the management of chronic liver disease. The recommended energy intake for cirrhotic patients is 1.2–1.4 times the resting energy expenditure of 21.9 ± 2 kcal/kg. A 30–33 kcal/kg ideal body weight (IBW) with 15–17% of energy from protein, 20–25% from fat, and the remainder (60–65%) from carbohydrate is recommended for energy intake in chronic liver disease as shown in Table 1. However, in advanced liver

Table 1. Recommended dietary energy and nutrient intake in compensated chronic liver disease

Energy (kcal/kg IBW/day)	30–33
Protein (g/kg IBW/day)	1.2–1.3
Fat (g/kg IBW/day)	0.8–0.9
Carbohydrate (g/kg IBW/day)	4.5–5.0
Energy ratio	
Protein (%)	15–17
Fat (%)	20–25
Carbohydrate (%)	60–65
α-Tocopherol (mg/day)	>10
α-Tocopherol /PUFA (mg/g)	>0.8
Vitamin C (mg/day)	>150
Iron (mg/day)	6–8
Zinc (mg/day)	12–15
PUFA/SFA ratio	1.0–1.2
n-6/n-3 PUFA ratio	2.8–3.2
Fiber (g/day)	20–25

disease, dietary manipulation may be necessary to compensate for the metabolic disorder.[6]

Protein restriction

Protein restriction has not only been advocated in the management of HE but it has been classically considered as the mainstay of treatment of HE. This appears to be a legacy from the era when oral protein restriction was one of the few treatment options available for HE. In a strictly protein-restricted diet, progression of protein energy malnutrition (PEM) has been found to be unavoidable. This led the researchers to look for an association between PEM and subclinical hepatic encephalopathy (SHE) and concluded that the restricted protein diet should only be given to the cirrhotic patients if the need is felt and that too with great caution. Results of the study showed that SHE is significantly linked to severe muscle depletion and not to severe fat depletion. Also, considering Child's classification by multivariate logistic regression, MAMC (mid-arm muscle circumference) <5 percentile was found to be a significant predictor of SHE.[7]

There is no major benefit of limiting protein intake on the evolution of episodic HE. In fact, the administration of a low-protein diet seems to exacerbate protein breakdown which may have detrimental consequences on the nutritional status

Further, nitrogen balance studies showed that there was a clear correlation in cirrhotics between protein intake and nitrogen balance and a higher protein intake is required to maintain a positive nitrogen balance in patients of HE. The data support the use of BCAA-enriched nutritious products to improve PEM in patients on protein-restricted diet.

Cordoba and colleagues designed a randomized study to assess the effects of protein in the diet in patients of HE.[8] Researchers enrolled patients from March 2001 to November 2002 and randomized them to two groups: 1) a low-protein group and 2) a normal protein group. The former received no protein for the first 3 days, protein intake was gradually increased every 3 days until 1·2 g/kg protein was received by patients in this group during the last 2 days. The normal protein group received 1·2 g/kg per day from the first day. Same amount of calories were given to all the patients throughout the study. Results of the study showed no significant difference in the course of HE between the two groups of treatment, neither among all patients enrolled in the study (Figure 1) nor the 20 patients who finished the 14

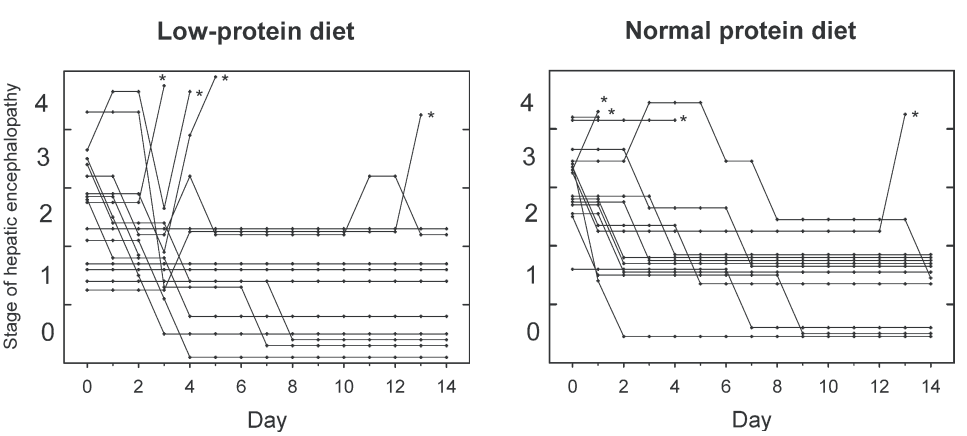

Figure 1. Evolution of hepatic encephalop thy in all patients randomized to follow the low-protein diet (upper panel) or the normal protein diet (lower panel). The asterisks identify those patients who died during the study.

days of treatment (Figure 2). The protein metabolism was analyzed in patients who completed the study. On the second day of therapy, protein breakdown was exacerbated in the low protein group (Figure 3) with no difference in protein synthesis. However these differences disappeared at the end of the study when the same group of patients received normal protein diet (1.2 g/day). Also, both groups showed similar values of plasma ammonia, prothrombin activity, bilirubin and albumin.

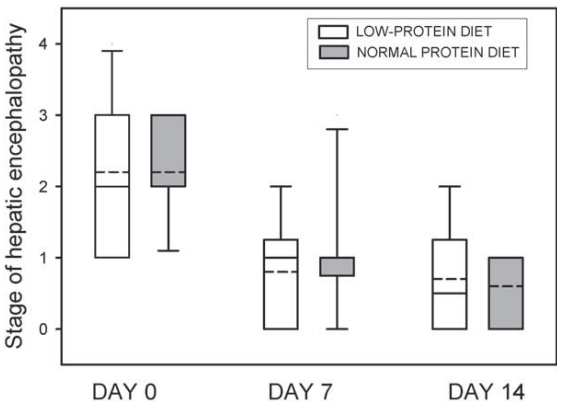

Figure 2. Stage of hepatic encephalopathy box plot: median, 10th-90th percentile, 25th-75th percentile, dashed line: mean at inclusion (day 0), day 7 and end of the study (day 14) in the patients that finished the study (per-protocol analysis), grouped according to treatment. There were no statistical differences between the low-protein diet (white boxes) and the normal protein diet (gray boxes).

Based on the results of the above study it is clear that there is no major benefit of limiting protein intake on the evolution of episodic HE. In fact, the administration of a low-protein diet seems to exacerbate protein breakdown which may have detrimental consequences on the nutritional status. The results suggest that patients with episodic HE can safely receive a normal protein diet. These results are in accordance with the current view that maintaining an adequate nutritional status is beneficial for patients with cirrhosis. Thus, administering enough protein to maintain protein requirements might even improve HE.

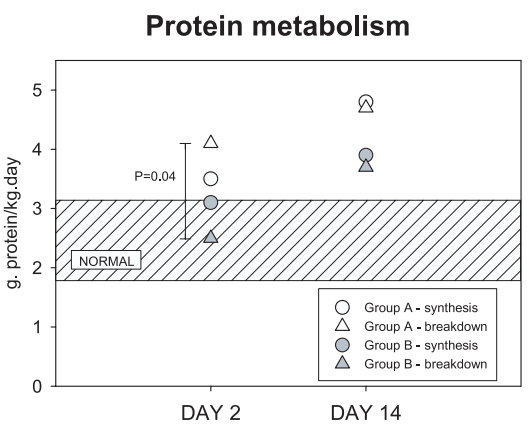

Figure 3. Protein metabolism (medians) estimated with the glycine-N15 method in patients who finished the study and followed the low-protein diet (group A) or the normal protein diet (group B). Protein breakdown at day 2 was higher in the low protein diet group (p 5 0:04). There were no statistically significant differences between baseline and final results in either groups. The figure shows the normal range observed in a previous group of healthy individuals [14] as a reference.

In addition, recent data confirm that an early introduction of oral protein at levels of 1.2 g/kg/day along with adequate oral calories does not delay recovery from HE which also supports the above conclusion.[9]

In another survey sent to 250 members of Ohio Board of Dietetics, results showed that dietitians fully completing the survey recommended a mean protein amount of 0.8 g/kg IBW/day ± 0.24, while dietitians within this group treating patients with HE within the past year, recommended a mean of 0.9 g/ kg IBW/day ± 0.24 which is lower than the recommended range by The European Society for Parenteral and Enteral Nutrition (ESPEN) and the American Dietetic Association (ADA). In addition, dietitians used ammonia as a biomarker for protein recommendations, and infrequently used BCAA-rich formulas or vegetable protein-rich diets. This survey reflects the existing gap between the previous belief and present day recommendation and suggests the need for continuing education of dietitians to promote optimal protein intake to HE patients, according to the recent guidelines.[10]

Recent data confirm that an early introduction of oral protein at levels of 1.2 g/kg/day along with adequate oral calories does not delay recovery from HE

Nitrogen balance studies showed that there was a clear correlation in cirrhotics between protein intake and nitrogen balance and a higher protein intake is required to maintain a positive nitrogen balance in patients of HE

Current recommendation

Despite the advice from experts in this field, many physicians still feel that protein restriction is desirable during the treatment of HE.[9] Irrespective of the recent data in support of the fact that limiting the amount of protein may worsen the clinical condition of these patients, this topic is controversial. The rationale for low-protein diet in the short- and long-term management of HE seems questionable in the current scenario. In view of the data from clinical studies, it seems logical that low-protein diets should be abandoned in favor of normal-protein diets in patients of HE. Protein restriction needs to be introduced only in malnourished patients with endstage liver disease who fail to maintain adequate oral nutrient intake.[6] The current recommendations advocate limiting protein restriction to short periods of time and early initiation of a normal protein diet in patients with episodic HE. Diets with a normal content of protein, which are metabolically more adequate, can be administered safely to cirrhotic patients with episodic HE. Restriction of the content of protein in the diet does not appear to have any beneficial effect for cirrhotic patients during an episode of encephalopathy.[8] The current recommendation is to limit protein restriction during an episode of HE to a moderate intake (0.5 g/kg/day) and to return to a normal-to-high protein intake (1–1.5 g/kg/day) shortly thereafter.[8] The ESPEN also acknowledges this fact and recommends that an adequate amount of protein should be given to HE patients (Table 2).[6]

Table 2 1997 ESPEN guidelines for nutrition in liver disease and transplantation

Clinical condition	Non-protein energy (kcal/kg body weight/day)	Protein or amino acid (g/kg body weight/day)
Compensated cirrhosis	25–35	1.0–1.2
Complicated cirrhosis		
Malnutrition	35–40	1.5
Encephalopathy I-II	25–35	0.5–1.5
Encephalopathy III-IV	25–35	0.5

The current recommendation is to limit protein restriction during an episode of HE to a moderate intake (0.5 g/kg/day) and to return to a normal-to-high protein intake (1–1.5 g/kg/day) shortly thereafter

Lowering nitrogenous load

Guidelines for the treatment of HE suggest ammonia reduction as the main focus, based on the strategies to reduce generation and absorption of ammonia in the colon.[11] This can be achieved by bowel cleansing, nonabsorbable disaccharides, antibiotics and other newer therapies like OA which have been used to enhance the metabolism of ammonia in splanchnic and peripheral tissues.[5] OA improves impaired ammonia detoxification by acting as a substrate for the urea cycle in the liver as well as for the synthesis of glutamine via transamination in the muscles. Preliminary experiences in acute and chronic HE have been encouraging with OA therapy.[11]

Kircheis G, *et al* conducted a study to investigate the effect of OA therapy on "extracerebral" nitrogen metabolism, brain metabolism and neurotransmission and concluded that OA treatment resulted in significantly lower blood (34% and 39%) and brain (42% and 22%) ammonia concentrations, significantly higher urea production (39% and 86%) and significantly smaller increases in brain glutamine and lactate concentrations than in controls.[12] All these results are known to have beneficial effects on the manifestations of hyperammonemia-induced encephalopathy.

Researchers investigated the therapeutic efficacy of OA in a randomized, double-blind, placebo-controlled clinical trial in 66 patients with cirrhosis, hyperammonemia, stable, overt, chronic HE, and in SHE.[13] Results showed that OA-treated group showed more pronounced and faster decrease in blood ammonia levels than the placebo group (Figure 4). In the placebo

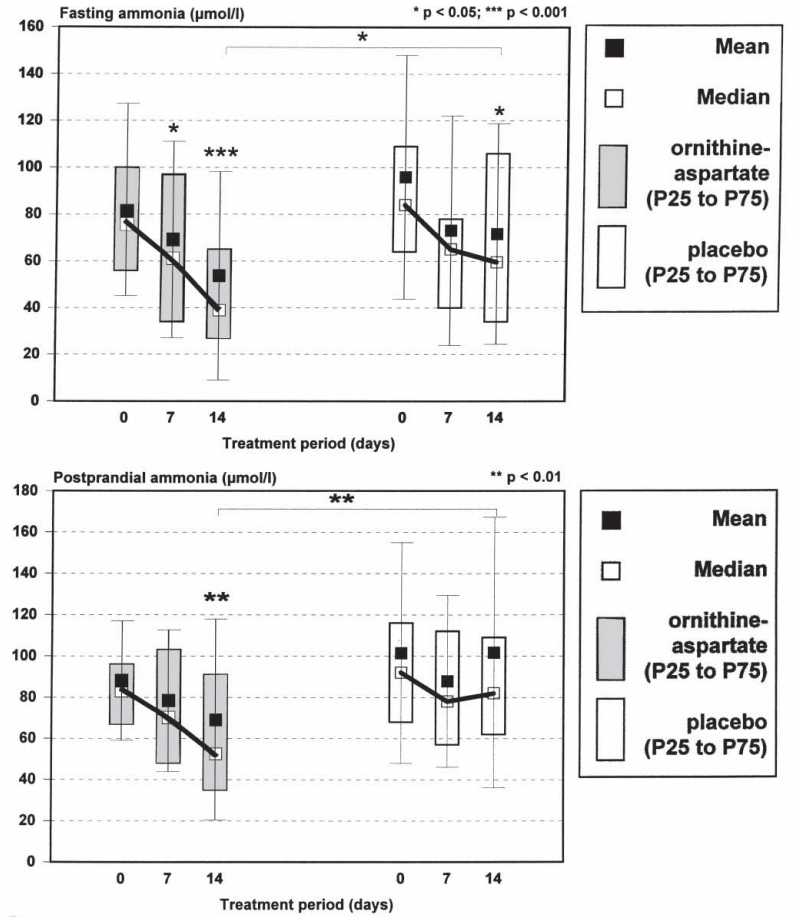

Figure 4. Effects of treatment with orally administered L-ornithine-L-aspartate (OA) or placebo on fasting as well as postprandial venous blood ammonia concentrations. P 25 and P 75 represent the 25th and 75th percentiles of the empiric distribution. 50% of the observed values are within this range. The group differences (Wilcoxon-Mann-Whitney test) and the pre-/post-differences within each group (Wilcoxon signed rank test) are presented within the two figures.

group, the number connection test (NCT) time remained same in the placebo group while it showed a continuous decrease in the OA-treated group . The mental state grade also improved significantly in the OA group. No drug reactions were seen in either of the groups. The results of this study confirm the already proven benefits of OA in patients of HE.[13] It seems that OA is a safe, well-tolerated treatment with a good compliance rate and a beneficial therapeutic effect in patients with cirrhosis and stable, overt, chronic HE.

In another randomized, double-blind, placebo-controlled clinical trial, researchers enrolled 126 patients with cirrhosis, hyperammonemia (>50 micromol/L), and chronic HE and found that OA is a safe and effective treatment of chronic manifest HE in cirrhotic patients.[14]

OA is a safe, well-tolerated treatment with a good compliance rate and a beneficial therapeutic effect in patients with cirrhosis and stable, overt, chronic HE

Conclusion

The treatment arena has seen some major advances and changing perspectives in the management of HE.[15] Current guidelines need to be revised with strict attention on treating the precipitating factors, with correction of dehydration, electrolyte and acid-base imbalance, constipation and infection. Low-protein diets for long duration should no longer be recommended as a standard care of HE. Reduction in hyperammonemia is the key to effective treatment of HE. Ornithine and aspartate are important substrates in the conversion of ammonia to urea, and administration of OA increases metabolism of ammonia and

reduces its concenteration leading to improvement of HE in cases with liver cirrhosis. It provides intermediates that increase glutamate availability, helps in detoxification of ammonia in the muscle and benefits the patients of HE. With these newer treatment modalities in the horizon there seems to be a ray of hope for patients of HE.

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