Review

Current concepts in the assessment and treatment of Hepatic Encephalopathy

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Summary

Hepatic encephalopathy (HE) is defined as a metabolically induced, potentially reversible, functional disturbance of the brain that may occur in acute or chronic liver disease. Standardized nomenclature has been proposed but a standardized approach to the treatment, particularly of persistent, episodic and recurrent encephalopathy associated with liver cirrhosis has not been proposed. This review focuses on the pathogenesis and treatment of HE in patients with cirrhosis. The pathogenesis and treatment of hepatic encephalopathy in fulminant hepatic failure is quite different and is reviewed elsewhere.

Introduction

Hepatic encephalopathy (HE) is defined as a metabolically induced, potentially reversible, functional disturbance of the brain. While HE may be a complication of acute or chronic liver disease, it is most commonly associated with cirrhosis. HE does not differ clinically from encephalopathies of other causes and, therefore, the diagnosis of HE requires the presence of liver disease or a portosystemic shunt. The two major mechanisms responsible for the development of HE are severe intrinsic hepatic dysfunction or the presence of portosystemic shunts leading to the diversion of portal blood to the systemic circulation before removal of toxic intestinal substances.¹ HE is characterized by personality changes, impaired intellect, disturbed sleep pattern and depressed level of consciousness. Following a consensus conference in 1998, HE is classified into three types—acute, recurrent or persistent—based on the underlying aetiology.² In the presence of chronic liver disease, HE is a marker of decompensation and as with other complications of liver disease, survival correlates better with the Child-Pugh score than the outcome of the complication itself. In fulminant liver failure, the development of HE is a worrying development and usually indicates that transplantation will be required.

Classifying and grading of hepatic encephalopathy

In 1998, the Working Party at the 11th World Congress of Gastroenterology proposed standardized nomenclature to distinguish types of HE.² Their final paper proposed three types—A, B and C (Table 1). The most common presentation of HE is the development of an acute confusional state that can lead to coma (acute encephalopathy).
This occurs in fulminant hepatic failure (type A) as well as patients with established cirrhosis (type C). In patients with cirrhosis, acute encephalopathy commonly results from a precipitating factor leading to a change in the mental state (Table 2). However, encephalopathy may develop in the absence of a precipitating factor (recurrent or episodic encephalopathy) and the neurological deficits seen may not fully resolve (persistent encephalopathy). Subtle signs of HE are present in nearly 70% of patients with cirrhosis, although the features may only be recognizable on neurophysiologic or psychometric testing (minimal or subclinical encephalopathy).

The degree of mental status disturbance in encephalopathy, classified by the West-Haven criteria, ranges from reversal of sleep patterns and mild alteration in cognition to deep coma (Table 3). Further classification of patients with coma or reduced level of consciousness is most reliably done using the Glasgow Coma Scale (GCS). While GCS has not been thoroughly examined in patients with HE, it provides a more objective assessment of the neurological impairment and it is less subject to observer variability. Calculation of the portal-systemic encephalopathy (PSE) score and index may also objectively describe the overall clinical severity of HE (Table 4). It is calculated following assessment of five elements—mental status, presence and intensity of asterixis, time taken to complete tests of intellectual function (such as number connection test), venous ammonia level and electroencephalogram (EEG) abnormalities. The grade for each of the five components is weighted in proportion to importance with mental status given a factor of 3, and the other four variables each assigned a factor of 1. A maximum PSE score of 28 indicates severe HE. The PSE index is expressed as the ratio of the patient’s PSE score to the maximum PSE score of 28. The PSE score and modified variations are primarily research tools and have not superseded the West-Haven criteria in clinical practice.

Pathophysiology

Despite much scientific research, the exact pathophysiological mechanisms leading to HE are not clearly understood. The most widely accepted theory of the pathogenesis of HE is that nitrogenous substances derived from the gut adversely affect the cerebral function. The main substance implicated is ammonia. The astrocyte, which accounts for 30% of cortical mass, is the only cerebral cell capable of metabolizing ammonia and is considered to be the cellular basis of the majority of changes in HE. Astrocytes are morphologically altered in HE and are swollen in acute liver failure. There is accumulating evidence that a number of pathophysiological mechanisms exist or co-exist; however, there is no doubt that increased ammonia concentration is integral in the pathogenesis of HE.

The ammonia theory

Ammonia has, for many years, been considered the main neurotoxin involved in the pathogenesis of HE. It is released from several tissues including kidney and muscle although its highest concentration is in the portal vein where it is derived from the colonic bacteria and metabolism of glutamine in the small bowel. In subjects with normal hepatocyte function, ~80–90% of ammonia is excreted through first pass metabolism. Excretion is reduced in both acute and chronic liver failure. The exact mechanism by which hyperammonaemia leads to HE remains uncertain; however, there is evidence that elevated intracellular ammonia levels result in altered neurotransmission mainly by agonizing gamma amino butyric acid (GABA) tone as well as causing cerebral energy...
Furthermore, ammonia detoxification in astrocytes leads to accumulation of glutamine, which is the main cause of astrocyte swelling.

In acute liver failure, glial swelling is also found along with overt cerebral oedema. The ammonia theory is given further credibility as most of the patients who develop HE have coexisting portosystemic collaterals in association with cirrhosis. Moreover, 90% of those with HE have elevated serum ammonia concentrations, and reductions in serum ammonia concentration are associated with improvement in HE grade. Despite these observations, there is a poor correlation between the serum arterial and venous concentration of ammonia and the grade of HE. The reason for this is unclear but may relate to increased cerebral uptake of ammonia in HE subjects, independently of the serum ammonia concentration. Experimental studies previously revealed a higher correlation between CSF glutamine and the degree of HE, but impairment of domains of cognitive function such as episodic memory and continuity of attention that occur in HE have recently been shown to correlate with serum ammonia concentration when assessed by computerized psychometric testing.

### GABA/benzodiazepine receptor complex theory

GABA is the main inhibitory neurotransmitter in humans and acts through binding to the GABA-receptor complex (GRC). Elevated levels of endogenous benzodiazepines as well as other neurosteroids lead to inhibition of neurotransmission. Changes in the GRC as well as cerebral GABA levels have also been reported in HE.

### BCAA and false neurotransmitter theory

Cerebral neurotransmission is regulated by CNS concentration of amino acids and their precursors. In patients with severe liver dysfunction, circulating plasma concentrations of aromatic amino acids (AAA) (tryptophan, tyrosine and phenylalanine) are elevated and branched-chain amino acids (BCCA) (leucine, isoleucine and valine) concentrations are reduced. AAA and BCCA share a common transport mechanism into the CNS and as a consequence of increased concentration of AAA, neuronal levels may be raised leading to the production of false neurotransmitters (octopamide and phenylethanolamide) with subsequent development of HE.
Serotonin theory

Serotonin, a neurotransmitter with widespread distribution in the CNS, has been implicated in the pathogenesis of HE. Changes in the synthesis, metabolism, storage and release of neuronal serotonin in HE suggest a serotonergic synaptic deficit. It is well established that cerebral serotonin is important for the regulation of sleep, circadian rhythmicity and locomotion. Serotonin metabolism is exquisitely and selectively sensitive to the degree of portosystemic shunting and hyperammonaemia, suggesting a role for serotonin in early neuropsychiatric symptoms of HE.

Zinc theory

Zinc, a substrate of urea cycle enzymes, may be depleted in patients with cirrhosis. Zinc supplementation increases the activity of ornithine transcarbamylase increasing excretion of ammonia ions. There is conflicting clinical data regarding zinc supplementation in the management of HE.

Manganese theory

Accumulation of manganese occurs in the basal ganglia of many patients with cirrhosis and reverses following liver transplantation. Serum manganese concentration correlates poorly with the degree of HE. Despite this, the similarity between the clinical manifestation of manganese intoxication and the extrapyramidal manifestations of HE suggests that elevated cerebral manganese levels play a role in the development of HE.

Treatment of hepatic encephalopathy

The mainstay of treatment of HE is supportive care, identification and treatment of precipitating factors, reduction in gut-derived nitrogenous products and identification of patients requiring long-term therapy.

Identification and removal of precipitating factors

Infection. Culture all appropriate body fluids. All patients with ascites should have a diagnostic paracentesis. Consideration should be given to a short course of empirical antibiotics in patients with hepatic coma pending culture results, particularly when no other obvious precipitant is identified.

Gastrointestinal haemorrhage. Prompt treatment of upper or lower GI bleeding is required.

Dehydration and electrolyte disturbances: acute renal failure following dehydration and the effect of diuretics may precipitate HE as may hypokalaemia, hypoglycaemia and metabolic alkalosis. In nutritionally deplete and alcoholic patients in particular, intravenous thiamine replacement should be commenced immediately.

Constipation: assessment of recent bowel habit is paramount. Ensure early institution of measures to produce adequate defaecation.

Medications. Assess for the use of psychoactive medications such as benzodiazepines and narcotics and discontinue if possible. Urine toxicology may be necessary. The use of chlordiazepoxide and other sedatives in drowsy cirrhotic patients who are at risk of delirium tremens should be limited to minimum possible dosages and withdrawn entirely if there is any deterioration in condition suggesting the development of encephalopathy.

Acute brain injury and seizures. A careful history and neurological examination should be undertaken to exclude focal neurological injury. If there is any doubt, a CT brain should be performed. Consideration should also be given to EEG analysis to exclude seizure activity or confirm the presence of typical slow, triphasic waveforms in the frontal lobes associated with HE.

Acute deterioration in liver function: uncommon in patients with established cirrhosis although seen in alcoholic hepatitis, acute circulatory disturbance (e.g. portal vein thrombosis) or following anaesthesia and surgery.

Specific measures

Diet. In the past, HE was managed by placing patients on protein restriction diets to reduce the production of intestinal ammonia. Recent evidence suggests that excessive restriction can raise serum ammonia levels as a result of reduced muscular ammonia metabolism. Furthermore, restricting protein intake worsens nutritional status and does not improve the outcome of HE. In patients with established cirrhosis, the minimal daily dietary protein intake required to maintain nitrogen balance is 0.8–1.0 g/kg. It is, therefore, now recommended that a normoprotein diet is administered to patients with HE. Patients intolerant to normal diet vegetable protein can safely substitute animal protein.

Drug administration. A nasogastric (Ng) tube should be inserted if a patient is too drowsy to swallow safely and drugs should be administered intravenously or Ng as appropriate. A history of oesophageal varices is not a contraindication to insertion.
Non-absorbable disaccharides. Lactulose reduces the concentration of aminogenic substrates in the colonic lumen in two ways—first by lowering the colonic pH through the production of organic acids by bacterial fermentation and second by a direct cathartic osmotic mechanism. The daily dose of lactulose is titrated to achieve two to three soft, acidic stools per day (pH <6), although in practice stool pH monitoring is not routinely performed. There are numerous studies evaluating the safety and efficacy of non-absorbable disaccharides in HE, but many of these are of poor design with only a small number of scientific merit and the largest of these studied incorporated only 26 patients. Despite the paucity of evidence, they are considered an established first-line therapy for HE, mainly due to many years of worldwide clinical experience. A systematic review of randomized trials assessing the use of non-absorbable disaccharides concluded that there is insufficient evidence to determine whether they are of benefit to patients with HE and that antibiotics appear to have superior efficacy. Other authors suggest that non-absorbable disaccharides have no role in the management of HE. Oral lactitol is an alternative to lactulose and is used in patients intolerant of lactulose in other countries, but is not available in the UK. It has been shown to be as effective as lactulose in the management of chronic HE.

Enemas. Enemas are commonly used in clinical practice, particularly in patients unable to take oral laxatives safely. Lactulose enemas have been shown to be efficacious in HE. For practical purposes, without evidence, phosphate enemas are often used in grade IV encephalopathy; however care should be taken to ensure that renal function is preserved if these are used regularly.

Antibiotics. Antibiotics directed to urease-producing bacteria have similar efficacy in HE to non-absorbable disaccharides. Neomycin is no longer recommended because of ototoxic and nephrotoxic side effects that result from the small percentage of the drug absorbed into the systemic circulation. The efficacy of metronidazole is similar to neomycin, but its long-term use is limited because of the gastrointestinal upset as well as the possibility of neurotoxicity.

Rifaximin, a non-absorbed derivative of rifamycin, has been studied as an alternative to neomycin. It has been shown to be well tolerated, safe and efficacious in both short- and long-term use in HE. The evidence is more substantial than for non-absorbable disaccharides and two recent trials adhering to Good Clinical Practice confirm that it is a useful alternative to disaccharides in patients with grades I–III HE. The recommended adult daily dose is 1200 mg/day, usually in three divided doses.

The combined use of non-absorbable disaccharides and antibiotic patients refractory to either agent alone is a subject of significant clinical relevance. The efficacy of combined therapy depends on the ability of the antibiotic-altered gut flora to metabolize lactulose. The limited data available suggest that the combination of lactulose and neomycin therapy was more effective than either agent alone. Studies comparing rifaximin and lactulose, either alone or in combination, have demonstrated that rifaximin is at least similar, and in some cases superior, in reversing encephalopathy than lactulose alone, with better tolerability reported in the antibiotic group.

LOLA. L-Ornithine L-aspartate (LOLA), a stable salt of ornithine and aspartic acid, provides crucial substrates for glutamine and urea synthesis, the key pathways in deamination. Experimental animal studies revealed reduced serum ammonia following oral administration of LOLA. In patients with cirrhosis and HE, oral LOLA leads to a reduction in serum ammonia as well as improvement in the clinical manifestations of HE. Measurable improvement of EEG activity has also been reported. One or two sachets of LOLA should be administered three times daily. The dose should be reduced in case of coexisting renal impairment.

Branched-chain amino acid supplementation. Altered amino acid metabolism is one of the hallmarks of advanced liver disease with reduced BCAA and increased AAA. It is widely believed that altered amino acid metabolism mediates many of the complication of HE including PSE as well as an overall reduction in nutritional status. The data regarding BCAA supplementations offer variable results—several small studies have reported improved biochemical profiles as well as reduction in HE grades although this has not been consistently reported. Two more recent randomized controlled trials of 820 patients demonstrated that long-term maintenance of BCAA supplementation led to a reduction in the rate of complications of cirrhosis as well as an overall reduction in hepatic failure. A significant improvement in overall nutritional status was observed.
Other treatments

Flumazenil. Based on the observation of increased GABA neurotransmitter tone, flumazenil has been studied. In a small number of patients, it results in a transient improvement in mental function. However, its use is limited to ruling out excess exogenous benzodiazepines as the cause of HE due to the overall poor efficacy.

Dopaminergic agonists. Bromocriptine and l-dopaa have been studied in cases of persistent HE with extrapyramidal features. As with BCAA, there remain a debate as to the efficacy of these agents and their use is not recommended in standard practice. Recent observations from neuroimaging and molecular studies indicate that cerebral deposition of manganese may underly the development of extrapyramidal features observed in HE. The use of manganese chelating agents has yet to be studied.

Molecular absorbent recirculating system (MARS). MARS is an extracorporeal artificial liver support system based on albumin dialysis. Its use in encephalopathy has been studied in a number of settings—in acute HE, it reduces the degree of cerebral oedema and the grade of HE in chronic HE. A recent meta-analysis of artificial and bioartificial liver support systems in patients with liver failure reported improvement in patients with acute-on-chronic liver dysfunction.

Acarbose. It is a novel hypoglycaenic agent that has been studied in type 2 diabetic patients with cirrhosis and grades 1 and 2 encephalopathy. It has been shown to improve intellectual function, ammonia levels and number connection test times. It remains unclear if the improvements seen in encephalopathy grade are due in part to improved glycemic control or if this drug is safe to administer to non-diabetic patients.

Probiotics. The rationale for the use of probiotics in HE is utilizing their fermenting potential to reduce the substrate for other bacteria in the gut. The results of initial trials assessing the effect of probiotics in HE are encouraging, including in minimal encephalopathy. Further studies are required; for now probiotics remain a second- or third-line treatment.

Discussion

The diagnosis and management of HE remain a difficult challenge for the medical professionals. Both the nature of the disease and the patient population suffering the illness have limited the number of large, quality trials assessing both pathophysiology and therapeutic options. Despite the limited number of therapeutic options available, there is often variability in management between specialized centres, with some centres opting for lactulose but not enemas whilst others choose LOLA over rifaximin. Based on the available evidence and clinical experience of our two centres, and in the absence of high-quality randomized controlled trials, the algorithm shown in Fig. 1 is suggested for the management of patients with HE.

Confirmation of the presence of a portosystemic shunt or advanced hepatic dysfunction should be sought initially. CT Brain, EEG and serum ammonia levels may be helpful in case of diagnostic doubt. Investigation for a reversible cause of HE in all cases and institution of general hospital supportive care including accurate fluid status assessment, regular monitoring, electrolyte status and regular neurological clinical assessment should follow. In comatose patients, airway protection should be sought and an NG tube inserted for the administration of medication and nutrition. A normal- or high-protein diet should be instituted with no role for dietary protein restriction. Administer bowel enemas for immediate effect, particularly in the drowsy or comatose patients. These should be continued twice daily until oral intake is established. A non-absorbable disaccharide, e.g. lactulose 30 ml three times daily, should be commenced as soon as is safe and the dose titrated to a bowel frequency of two to three loose motions per day. If there is not complete resolution of the encephalopathy in the following 24 h, rifaximin (1200 mg in three divided dose over 24 h) or LOLA (three to six sachets daily in three divided doses) should be added. Consider alternative non-absorbable antibiotics if there is a contraindication to rifaximin. Consideration should be given to the concurrent use of lactulose, rifaximin and LOLA in persistent HE despite the aforementioned measures. Branch-chain amino acids, flumazenil and dopaminergic have little role to play in the management of HE, but may be used in the event of resistance to the above measures and in the absence of an obvious ongoing precipitant. Similarly, MARS has no role to play at present in the daily care of encephalopathic patients on general medical units but may be considered useful in specialized units as a bridge to transplantation.

Patients suffering from HE are found in almost every hospital. Identifying both the illness and its precipitants are crucial to rapid resolution. It is clear that little progress has been made in developing new therapeutic options over the last 20 years, but optimal use of the simple measures described...
earlier significantly improves the impact and morbidity associated with HE.

Conflict of interest: None declared.

References


