Hepatic encephalopathy

Hepatic encephalopathy is a serious complication of both acute and chronic liver failure. It manifests as a spectrum of neuropsychiatric symptoms which are associated with significant morbidity and mortality. This review discusses salient underlying pathogenic mechanisms and highlights diagnostic paradigms and management strategies.

Hepatic encephalopathy is a serious and potentially fatal complication of both acute and chronic liver disease, arising as a result of hepatocellular failure, cirrhosis and/or portal-systemic shunting (Ferenci et al, 2002). It reflects a broad spectrum of neuropsychiatric abnormalities, encompassing a range of defects in psychomotor, locomotive, cognitive, emotional and behavioural functions (Prakash and Mullen, 2010). Hepatic encephalopathy is either overt or minimal. While overt hepatic encephalopathy can be diagnosed using bedside clinical tests, minimal hepatic encephalopathy is clinically invisible and requires psychometric testing to diagnose. The rising prevalence of end-stage viral hepatitis-related liver disease, coupled with the growing problem of alcoholic and non-alcoholic fatty liver disease, has significantly increased the burden of disease from cirrhosis (Mooney et al, 2007; Fleming et al, 2008), so recognition and appropriate management of the manifestations of decompensating cirrhosis (including hepatic encephalopathy) is essential. Hepatic encephalopathy has a substantial societal burden because of its impact on survival, quality of life and daily functioning, including an impaired ability to drive, leaving patients especially vulnerable to road traffic accidents (Ferenci et al, 2002; Prakash and Mullen, 2010).

Nomenclature

According to international consensus guidelines hepatic encephalopathy is classified into type A (caused by acute liver failure), B (caused by portosystemic bypass) or C (caused by cirrhosis) (*Table 1*). Type C is the most frequently encountered (Ferenci et al, 2002; Mas, 2006).

Pathophysiology

The pathogenesis of hepatic encephalopathy in acute liver failure is well described as hyperammonaemia can cause osmotic disturbances in the astrocyte, which leads to overt cerebral oedema and hepatic encephalopathy. However, the precise pathophysiological mechanisms have not yet been fully elucidated in type C hepatic encephalopathy occurring slowly on the background of chronic liver disease. A multifactorial model has been proposed, although the relative contributions of different molecular mechanisms continue to be disputed. Some of the important issues are discussed below.

Ammonia

The metabolism of nitrogen-containing compounds releases ammonia. Ammonia is metabolized via the urea cycle to urea, which is excreted via the kidneys. However, liver failure can impair urea cycle function. Subsequently, extrahepatic organs, in particular the brain, become 'ammonia sinks' (Shawcross and Jalan, 2005b). Astrocytes are a site of conversion for ammonia to glutamine, and as ammonia concentration increases, intracellular glutamine levels rise. Glutamine is an osmolyte and draws water into the astrocyte, causing it to swell, leading to cerebral oedema (Larsen and Wendon, 2002; Prakash and Mullen, 2010). However, more recent observations have cast doubt on this theory. A study using rats with acute liver failure showed glutamine levels correlated poorly with the degree of swelling, while Jayakumar et al (2006) found that maximal astrocyte swelling paradoxically occurred when glutamine levels were low. Therefore, it has been suggested that glutamine acts as a 'Trojan horse' and enters the mitochondria of astrocytes, where it is converted back to ammonia, which causes subsequent swelling and generation of reactive oxygen species.

High levels of mitochondrial glutamine, coupled with oxidative stress, activate the mitochondrial permeability transition, which leads to collapse of the inner mitochondrial membrane potential. The activation of mitochon-

Table 1. Classification of hepatic encephalopathy

Type	Nomenclature	Subcategory	Subdivisions
A	Acute liver failure		
B	Portosystemic bypass, no intrinsic hepatocellular disease, e.g. portal vein thrombosis		
C	Cirrhosis and portal hypertension or portal-systemic shunts	Episodic	Precipitated, spontaneous, recurrent
		Persistent	Mild, severe, treatment-dependent
		Minimal	

From Ferenci et al (2002)

Ms D Patel *is Medical Research Associate,* **Dr MJW McPhail** *is Wellcome Clinical Fellow in Gastroenterology,* **Dr JFL Cobbold** *is Clinical Lecturer in Hepatology and* **Professor SD Taylor-Robinson** *is Professor of Translational Medicine in the Department of Medicine, Hepatology and Gastroenterology Section, Imperial College London, St Mary's Hospital Campus, London W2 1NY*

Correspondence to: Professor SD Taylor-Robinson (s.taylor-robinson@imperial.ac.uk)

drial permeability transition and production of reactive oxygen species in turn leads to the activation of cell signalling pathways which culminates in an inability of astrocytes to regulate their intracellular volume, ultimately leading to cerebral oedema (Zwingmann et al, 2003; Albrecht and Norenberg, 2006; Jayakumar et al, 2006).

Neuroinflammation

Sepsis is a well-recognized precipitant for acute-on-chronic liver failure. Shawcross et al (2004) investigated the effect of induced hyperammonaemia in ten patients with cirrhosis who were admitted with systemic inflammatory response syndrome. Induced hyperammonaemia resulted in a worsening of neuropsychometric scores in the presence of systemic inflammation, mediated by pro-inflammatory cytokines including tumour necrosis factor-alpha, interleukin-1 and interleukin-6. However, psychometric test results did not deteriorate further once systemic inflammatory response syndrome had been treated and the previously elevated cytokines had returned to normal, thus providing direct evidence for the role of inflammation in the pathogenesis of hepatic encephalopathy. Furthermore, in patients with acute liver failure, cerebral production of pro-inflammatory cytokines correlates well with uncontrolled intracranial hypertension, indicating activation of the inflammatory cascade (Wright et al, 2007). It is likely that the brain is responding to the systemic inflammatory response syndrome, which in acute liver failure assists in inducing intracranial hypertension via reduced permeability of the blood–brain barrier, and in type C hepatic encephalopathy, systemic cytokine release is a likely co-factor in inducing encephalopathy in conjunction with microglial activation. Studies in rats have demonstrated this finding, showing that raised blood levels of tumour necrosis factor, as occurs during systemic inflammation, stimulate glial cell secretion of pro-inflammatory cytokines (Moldawer et al, 1989).

Gamma aminobutyric acid and benzodiazepine

Gamma aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. Benzodiazepines act on the GABA receptor complex to cause neuroinhibition. Enhancement of GABA-ergic tone has been implicated in the pathophysiology of hepatic encephalopathy (Albrecht and Jones, 1999; Jones, 2000), as a consequence of increased endogenous benzodiazepines. Intestinal flora can also contribute by providing precursors, which are converted into natural benzodiazepines in the brain (Faint, 2006; Mas, 2006). Although it was originally thought that an augmented tone was caused either by a combination of decreased hepatic metabolism and increased transmission of GABA across the blood–brain barrier (Bassett et al, 1990), or by alterations in the $GABA_A$ receptor complex (Ahboucha et al, 2003), both these mechanisms have since been refuted (Ahboucha and Butterworth, 2004).

Branched chain amino acids

Branched chain amino acids, such as leucine, isoleucine and valine, and aromatic amino acids, such as phenylalanine, tryptophan and tyrosine, are competitively taken up across the blood–brain barrier. Porto-systemic shunting results in both an absolute rise in plasma concentration of aromatic amino acid, as the liver is the chief site of their degradation (James, 2002), and a rise relative to that of branched chain amino acids. This is because, in liver failure, skeletal muscle is used as an ammonia sink to detoxify ammonia through conversion to glutamine. This results in a fall in branched chain amino acid levels. Therefore, higher levels of aromatic amino acids enter the brain, where they act as substrates for the synthesis of neuroactive substances, such as tryptophan and serotonin, which may be harmful in excess (Faint, 2006).

Investigation of hepatic encephalopathy

A detailed history is essential to determine the aetiology of the underlying liver disease, in order to ascertain whether hepatocellular failure is a result of acute liver failure or chronic liver disease.

The classical definition of acute liver failure, coined by Trey and Davidson (1970), describes hepatic failure occurring in the absence of pre-existing liver disease with an update on the time course of the disease given by O'Grady et al (1993). Acute liver failure can progress quickly to coma and death from cerebral oedema. History should ascertain the cause of liver failure as this may affect management. Investigations ideally should include serial ammonia readings, which should be expected to be well above the normal range, and computed tomography imaging, which can help assess degree of cerebral oedema, a poor prognostic indicator. Magnetic resonance imaging is not usually indicated, particularly if the patient is progressively deteriorating, as in many centres there is often difficulty with anaesthetic or resuscitation equipment for very sick patients in a magnetic resonance imaging environment. Immediate liver transplant is critical to the survival of these patients, and contact with a regional transplant centre should be made early on.

Type C hepatic encephalopathy, by contrast, tends to be characterized by a chronic and often fluctuating encephalopathy. The approach to diagnosis of hepatic encephalopathy initially requires the exclusion of other conditions which can mimic hepatic encephalopathy and the identification of potential precipitating factors, principally sepsis, gastrointestinal bleeds, drugs and constipation (*Tables 2* and *3*). History and examination should elicit the severity of chronic liver disease, as specific clinical signs may be observed (*Figure 1*). Jaundice and ascites may be present in conjunction with hepatic encephalopathy, reflecting decompensated chronic liver disease. Although asterixis is not specific to hepatic encephalopathy, it is commonly seen in chronic liver disease potentially as a result of disturbance to the basal ganglia. A patient who is not able to raise his/her hands

up to demonstrate adequately a 'flapping tremor' can be assessed by the examiner passively dorsiflexing the patient's wrists or gripping the hands. Asterixis is confirmed by an oscillatory grip, which fluctuates between tight and loose (Bajaj, 2010).

Initial assessment should include a formal assessment of mental status, usually by way of mini mental state examination. The suggested algorithm by Stewart and Smith (2007) indicates that further neuropsychological testing is indicated in patients with a score greater than 24, in order to detect minimal hepatic encephalopathy. Those with a score less than 24 may have a diagnosis of overt hepatic encephalopathy. Neuropyschological assessments broadly encompass four categories: clinical assessment scales, neuropsychometric tests, which comprise 'paper and pencil' tests and computerized tests, neurophysiological assessments, and brain imaging (Bajaj et al, 2009; Prakash and Mullen, 2010).

Neuropsychometry

Overt hepatic encephalopathy is typically graded using clinical scales, the most widely used being the West Haven criteria (*Table 4*) (Conn and Bircher, 1994). However, the most reproducible stages of assessment tend to be above grade 2. By contrast, diagnosis of minimal hepatic encephalopathy requires specialized neuropsychometric tests, as these patients tend to have cognitive dysfunction in the absence of clinical features indicative of overt hepatic encephalopathy.

Table 2. Differential diagnosis of encephalopathy

Subdural haematoma	
Sepsis	
Metabolic derangements	Hypoxia
	Acidosis
	Electrolyte abnormalities
	Hypoglycaemia
	Uraemia
Toxins	Psychoactive drugs
	Heavy metals
Prior alcohol abuse	Delirium tremens
	Wernicke–Korsakoff syndrome

Table 3. Precipitating factors for hepatic encephalopathy

Infection	Sepsis
Electrolyte abnormalities	Diarrhoea
	Vomiting
	Dehydration
Iatrogenic interventions	Drugs – diuretics, benzodiazepines
	Radiological stent insertion
Gastrointestinal haemorrhage	
Constipation	

Figure 1. Pathogenesis of hepatic encephalopathy. Adapted from Shawcross and Jalan (2005a).

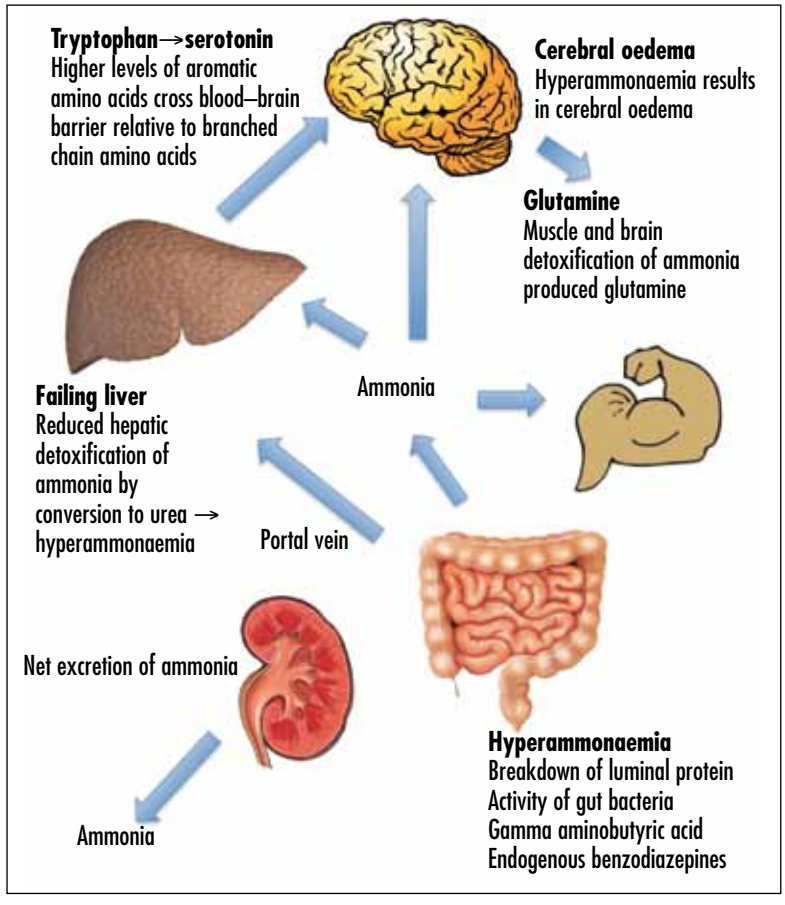


Table 4. West Haven criteria

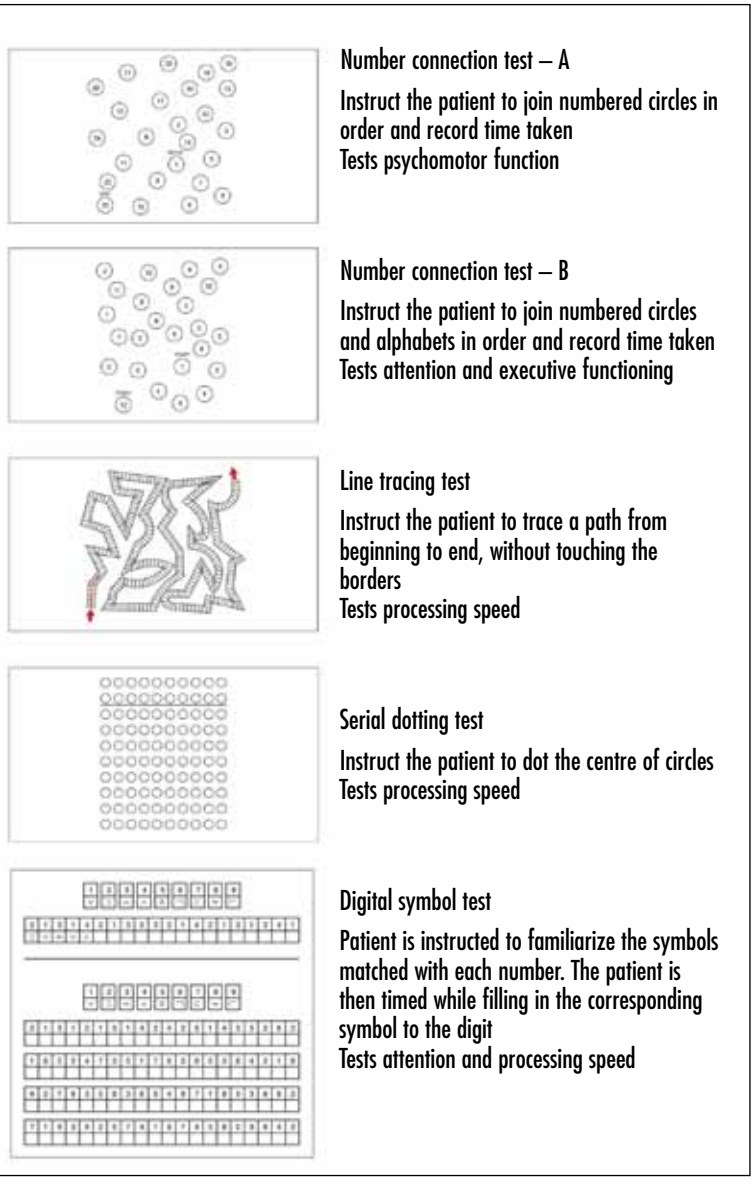
Grade 0	No abnormality detected
Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition and subtraction
Grade 2	Lethargy or apathy
	Minimal disorientation in time or place
	Subtle personality change
	Inappropriate behaviour
	Asterixis
Grade 3	Somnolence to semi-stupor
	Confusion
	Gross disorientation – responds to verbal stimuli
Grade 4	Coma – does not respond to verbal or noxious stimuli

From Conn (1994)

Neuropsychometric testing focuses on attention span, short-term memory and executive functioning as these cognitive domains tend to be impaired in minimal hepatic encephalopathy. The psychometric hepatic encephalopathy score is a five-part bedside test, which can be performed easily in the clinical setting by the supervising clinician (*Figure 2*). It has a high specificity for detection of minimal hepatic encephalopathy and has been internationally endorsed as the 'gold standard' for diagnosis of minimal hepatic encephalopathy in Europe (Weissenborn et al, 2001).

Of the computerized assessments, the system designed by Cognitive Drug Research, Goring-on-Thames, UK, has been shown to correlate well with the psychometric hepatic encephalopathy score test, and is used in the UK (Mardini et al, 2008). However, it is not as suitable for the bedside as the psychometric hepatic encephalopathy score test, so is used primarily in research settings (Ferenci et al, 2002; Stewart and Smith, 2007; Bajaj et al, 2009). The Repeatable Battery for the Assessment of Neurological Status is a pencil-and-paper test, similar to the psychometric hepatic encephalopathy score, which can be used to evaluate a spectrum of neurocognitive disorders including dementia, schizophrenia and multiple sclerosis (Prakash and Mullen, 2010). Its use in assessing liver disease is largely confined to the USA, where it is the gold standard (Randolph et al, 2009). The Repeatable Battery for the Assessment of Neurological Status assesses domains similar to the psychometric hepatic encephalopathy score, such as memory, cognition, language and visuo-spatial function, and scores correlate well with model for end stage liver disease scores in US cohorts (Sorrell et al, 2006). However, it is time-consuming to perform and usually requires a trained psychologist to administer the test battery, which somewhat limits its utility in the clinical practice of the average gastroenterologist or hepatologist.

Figure 2. Five components of psychometric hepatic encephalopathy score testing.



Neurophysiological tests

These range from a simple electroencephalogram to advanced techniques of evoked potentials. A reduced level of neural electrical activity is seen in patients with hepatic encephalopathy, and typical electroencephalogram findings demonstrate 'triphasic waves' (Bajaj et al, 2009; Prakash and Mullen, 2010). Although this is not a finding specific to hepatic encephalopathy, electroencephalography is useful where there is diagnostic uncertainty, or in situations where a diagnosis of hepatic encephalopathy must be excluded, for instance before procedures such as transjugular portosystemic stent shunts.

The critical flicker frequency was developed as a psychophysical assessment, which does not require psychological expertise. It assesses the frequency threshold at which a flickering light is still observed as flickering rather than continuous, and reflects functional efficacy of the cortex. Critical flicker frequency is generally unaffected by the age, educational background and training of patients, yet is able to detect a wide spectrum of neuropsychological impairments. However, the technique cannot reliably distinguish patients with minimal hepatic encephalopathy from patients without hepatic encephalopathy, and at present it is not known whether critical flicker frequency values reflect disruptions to quality of life and whether it can be used to serially assess severity of disease (Haussinger and Schliess, 2008; Bajaj, 2010).

Neuroimaging

This is only used as an adjunct in the diagnosis of type B and C hepatic encephalopathy. Although magnetic resonance imaging can detect cerebral oedema, even at a low grade, it is not often used in the diagnostic work-up of acute liver failure because there is a clear clinical diagnosis or because of safety concerns regarding prolonged horizontal positioning while scanning. Hyperintensity in the basal ganglia, attributed by some to manganese deposition in the globus pallidum, has been reported on T1-weighted

magnetic resonance imaging from patients with cirrhosis (Taylor-Robinson et al, 1995). Although it is seen in the majority of patients, this observation is not pathognomonic of hepatic encephalopathy as cholestasis with consequent impaired biliary manganese excretion can give the same observation. A computed tomography scan of the head may also be useful in excluding alternative pathology such as a subdural haematoma. Other forms of brain imaging including single positron emission computed tomography and positron emission tomography scans, and magnetic resonance spectroscopy are more suited to research purposes at present (Berding et al, 2009).

Ammonia levels

Although ammonia has been implicated in the pathogenesis of hepatic encephalopathy and is useful in acute liver failure, there is a limited role for measurement of ammonia levels in chronic liver disease. Routine assessment of ammonia levels is not advised as it does not influence management, and a single measurement does not correlate well with the severity of hepatic encephalopathy in chronic liver disease (Morgan et al, 1982; Bass, 2007). If used, an arterial sample should be taken with immediate testing or transport to laboratory facilities on ice.

Treatment of hepatic encephalopathy

The aims and outcome of treatment depend on the severity and grade of encephalopathy. At present, there is a paucity of data to support treatment of minimal hepatic encephalopathy. By contrast, the management of overt hepatic encephalopathy is better defined and can be discussed in terms of both acute and long-term therapy. In the short term, the goals of treatment comprise supportive measures, identification and elimination of precipitating factors (*Table 3*) – which should be treated and reversed as a priority –, and assessment of need for liver transplantation. Long-term treatment aims to control precipitating factors, prevent recurrent episodes and improve daily functioning (Blei et al, 2001; Prakash and Mullen, 2010).

Therapies for hepatic encephalopathy target aspects of its pathogenesis. These include reducing production and absorption of ammonia, inhibiting central $GABA_A$ receptors, and decreasing generation of false neurotransmitters.

Pharmacological therapies

Non-absorbable disaccharides

Lactulose is a prebiotic and an example of a non-absorbable disaccharide. It is considered to be first-line therapy in patients with hepatic encephalopathy. These drugs have a laxative effect, which reduces the nitrogenous load from the gut. In addition, lactulose can lower the colonic pH, which produces an inhospitable environment for urease-producing bacteria, thus reducing luminal ammonia synthesis and absorption (Riordan and Williams, 2008). However, approximately 5% of patients suffer side effects so severe they discontinue treatment. Although lactulose is poorly tolerated, a meta-analysis investigating the effects of prebiotics, probiotics and synbiotics in minimal hepatic encephalopathy showed lactulose as an individual agent to have the most beneficial effect, with all three categories of therapy contributing to a significant clinical improvement, giving strong evidence for their use in this group of patients (Shukla et al, 2011).

Antibiotics

Antibiotics with activity against urease-producing bacteria have proven value in treating hepatic encephalopathy, as they reduce ammonia production. Rifaximin is a non-absorbable antibiotic with broad-spectrum activity against both aerobic and anaerobic Gram positive and Gram negative bacteria (Bass et al, 2010). Since gaining approval from the Food and Drug Administration in March 2010, it has been widely used in the USA, as a result of its beneficial effects including reversal of hepatic encephalopathy, and improvements in cognitive function and health-related quality of life parameters (Sidhu et al, 2011). Bass et al (2010) demonstrated the utility of rifaximin in both maintaining remission from minimal hepatic encephalopathy and reducing risk of hospitalization subsequent to hepatic encephalopathy. Minimal hepatic encephalopathy adversely affects daily activities, especially ability to drive, and rifaxamin also improves driving simulator performance in affected patients (Bajaj et al, 2011).

Other antibiotics, such as neomycin and vancomycin, can be prescribed, but are associated with adverse effects such as ototoxicity and nephrotoxicity (Riordan and Williams, 2008).

Other therapies

Other pharmacological interventions include L-ornithine-L-aspartate and sodium benzoate, which aim to increase metabolism of ammonia by providing alternative detoxification pathways. A meta-analysis showed that while L-ornithine-L-aspartate is effective in patients with overt hepatic encephalopathy, particularly grades I or II, it is less useful in patients with minimal hepatic encephalopathy (Jiang et al, 2009). The benzodiazepine receptor antagonist, flumazenil, has been used, but there are concerns over its potential to decrease the threshold for seizures (Riordan and Williams, 2008; Bajaj, 2010), and it is not recommended.

Nutritional therapies

Vegetable-based protein: Contrary to previous reports, patients with hepatic encephalopathy should not be protein restricted. They are often in a catabolic state and require 1–1.5 g/kg of protein per day. Vegetable protein tends to be better tolerated than meat protein. In addition, vegetable proteins increase intestinal transit time and colonic motility as a result of their high fibre content, as well as improving faecal nitrogen output (Riordan and Williams, 2008; Prakash and Mullen, 2010). However, the clinical utility of a vegetable protein-based diet is limited by poor patient compliance and is not used routinely in many centres.

Branched chain amino acids: The administration of preparations high in branched chain amino acids and low in aromatic amino acids is based on reducing transmission of aromatic amino acids across the blood–brain barrier, thus reducing the production of false neurotransmitters which can contribute to encephalopathy (Riordan and Williams, 2008). Although branched chain amino acids improve recovery and reduce duration of hospital admissions (Muto et al, 2005), a Cochrane systematic review of 11 randomized trials found that branched chain amino acids did not have a significant beneficial effect on patients with hepatic encephalopathy. Studies involving branched chain amino acids tend to be limited by short follow-up periods and poor methodological quality (Als-Nielsen et al, 2003). Furthermore, they are expensive and may not always be readily available. However, higher quality studies are required in this area.

Prebiotics, probiotics and synbiotics: Prebiotics are a non-digestible food ingredient which stimulates the growth of select colonic bacteria to improve host health whereas probiotics are a live microbial food supplement which improves host gut microbial balance, and synbiotics are a combination of the two. A meta-analysis showed that supplementing the diet with pre-, pro- and synbiotics can lead to significant improvements in patients with minimal hepatic encephalopathy, suggesting that their inclusion may have clinical benefits. The supplements were well tolerated with no major adverse effects reported (Shukla et al, 2011).

Orthotopic liver transplantation

Orthotopic liver transplantation is the definitive treatment for hepatic encephalopathy arising as a result of both acute liver failure and chronic liver disease. However, its urgency depends on the cause and nature of liver failure. In patients with acute liver failure who are progressing to cerebral oedema and hepatic encephalopathy, an orthotopic liver transplantation is crucial to survival and urgent discussion with a liver transplant centre is required as patients can deteriorate to cerebral coning and brain death. In patients with chronic liver disease, hepatic encephalopathy tends to be chronic and fluctuating, and is considered to be one of the cardinal manifestations of decompensating liver disease. Orthotopic liver transplantation in this group of patients tends to be determined according to need and prospective survival via established chronic liver disease criteria (Neuberger et al, 2008).

Strategies for long-term management

The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver have commissioned a joint working party on management algorithms in hepatic encephalopathy, which should report in November 2012. Since there is currently a lack of consensus on long-term treatment strategies, and pending the report of the expert working party, a simple stepwise approach to long-term management is proposed. Following an episode of hepatic encephalo-pathy, patients with cirrhosis usually remain on empirical therapy (lactulose) for an indefinite period of time, although adverse effects caused by lactulose may affect adherence, or until patients receive an orthotopic liver transplantation. Despite its adverse effects, the authors suggest using lactulose as first-line treatment, followed by rifaximin, in accordance with the latest evidence, and then L-ornithine-L-aspartate (Bass et al, 2010; Sidhu et al, 2011). Clinicians should aim for a normal mini mental state examination score with stable maintenance therapy. If successful, this should prevent further episodes of hepatic encephalopathy and allow patients to continue with daily functioning (Bajaj, 2010). Chronic relapsing or remitting overt hepatic encephalopathy tends to be episodic and can be treated relatively simply as it is more easily recognized, although in some cases overt hepatic encephalopathy may run a more persistent course.

Although minimal hepatic encephalopathy is a subclinical condition with significant effects on activities of daily living, such as driving and operating machinery, there is a lack of consensus on the importance of treatment in minimal disease. However, given the evidence on the societal effect that patients with minimal hepatic encephalopathy exhibit (Bajaj et al, 2011), many authorities are coming round to the idea that long-term treatment may be required, at least in those patients who have significant psychomotor retardation on neuropsychological testing. On the other hand, given the difficulties with neuropsychological testing in the clinical arena, some advocate that there would be no harm in offering at least lactulose treatment to all patients with cirrhosis, even though this may over-treat the minority of patients without minimal hepatic encephalopathy, as most patients would be safely treated in an appropriate fashion.

Conclusions

Hepatic encephalopathy is a neuropsychiatric syndrome whose symptoms exist on a continuum. Early recognition and management is important in optimizing outcome, particularly in the context of the timing of orthotopic liver transplantation. With the right treatment, most patients with overt hepatic encephalopathy can lead relatively normal lives with reasonable neuropsychological function, provided that their underlying liver function is stable and that precipitating factors, such as variceal bleeding and infections, are addressed promptly. However, in the acute setting, hepatic encephalopathy is the hallmark of acute liver failure and urgent orthotopic liver transplantation may be required. **BJHM**

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KEY POINTS

- Hepatic encephalopathy defines acute liver failure and is a common but treatable complication of cirrhosis.
- Progressive hepatic encephalopathy in acute liver failure is an important poor prognostic sign warranting urgent referral to a liver transplant centre.
- Minimal hepatic encephalopathy is an important variant of hepatic encephalopathy in cirrhosis which can only be diagnosed by psychometric evaluation.
- Rifaximin is a recent addition to the treatment for hepatic encephalopathy in patients with otherwise well-compensated cirrhosis.