Diagnosing and treating hepatic encephalopathy

Hepatic encephalopathy is a complex condition. This article considers the efficacy of the methods used in its diagnosis and management and discusses the impact of minimal hepatic encephalopathy on patients and the ethics of its treatment.

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Hepatic encephalopathy is a neuropsychiatric condition, resulting from hepatocellular failure and/or portosystemic shunting (Kato et al, 2008). It encompasses alterations in cognitive, emotional, behavioural and motor functions. Hyperammonaemia is a contributing factor, in addition to neuroinflammation, acting in synergy to cause astrocyte swelling and intracellular fluid accumulation in the brain (Ferenci et al, 2002; Vilstrup et al, 2014).

In 1998, the Working Party for Hepatic Encephalopathy designed a classification system for hepatic encephalopathy (Prakash and Mullen, 2010):

- Type A – associated with acute liver failure
- Type B – associated with portal systemic bypass without intrinsic hepatocellular disease
- Type C – associated with chronic liver disease or portal systemic shunts, divided into episodic, persistent and minimal hepatic encephalopathy,.

Hepatic encephalopathy severity is graded using West Haven or SONIC (spectrum of neurocognitive impairment in cirrhosis) criteria (*Table 1*).

Overt hepatic encephalopathy has protean clinical signs and symptoms, whereas minimal hepatic encephalopathy is more subtle, showing no clinical signs. Minimal hepatic encephalopathy is thus difficult to detect, with deficits in cognition discernible on neuropsychometric or neurophysiological testing. The term 'minimal' is somewhat misleading because minimal hepatic encephalopathy does predict the development of overt hepatic encephalopathy and has a substantial burden on health-related quality of life and activities of daily living, such as driving (Prakash et al, 2013).

Minimal hepatic encephalopathy is present in over 60% of patients with cirrhosis, and recognizing hepatic encephalopathy is important, although the average clinician is usually inexpert in this area (Prasad et al, 2007; Fleming et al, 2008). There is currently no consensus defining the

Table 1. Grading of hepatic encephalopathy severity using West Haven or SONIC classification

West Haven grading	Type of impairment		SONIC classification
	Cognitive	Neuromuscular	
0	Normal	Normal	Normal
Minimal hepatic encephalopathy	Normal examination, very subtle changes in work or driving	Minor abnormalities on psychometric or number tests or on visual perception	Minimal (covert)
I	Personality change, irritable, poor attention, depressed state	Tremor, decreased coordination	Minimal (covert)
II	Changes in sleep–wake cycle, lethargy, mood and behavioural changes, cognitive dysfunction	Asterixis, ataxic gait, speech abnormalities	Overt
III	Reduced level of consciousness, confusion, disorientation, amnesia	Rigidity and clonus, nystagmus, Babinski's sign, hyperreflexia	Overt
IV	Reduced level of consciousness to stupor or coma	Unresponsiveness to noxious stimuli, oculocephalic reflex	Overt

From Leise et al (2014)

most appropriate tool for detection of minimal hepatic encephalopathy, nor on the value of routine testing. Pencil/paper or computerized neuropsychometric tests and neurophysiological tests such as electroencephalograms, evoked potentials and critical flicker frequency are all proposed methods (Ferenci et al, 2002; Vilstrup et al, 2014). Similarly, management of minimal hepatic encephalopathy proves difficult because of the lack of clinical signs. Current treatments focus on removal of bacteria-derived toxins and modulation of gut flora using probiotics, non-absorbable disaccharides and antibiotics (Leise et al, 2014).

Common side effects produced by treatments for hepatic encephalopathy raise ethical questions concerning management of patients with asymptomatic minimal hepatic encephalopathy. However, because of the potential driving impairment, these patients may pose societal risks. 'Catch-all' lactulose treatment for all patients with cirrhosis has been suggested, despite the potential to treat patients without any form of hepatic encephalopathy. The pathogenesis, diagnosis and treatment of hepatic encephalopathy is discussed, with analysis of the ethical implications of treatment.

For the purpose of this review, a literature search was conducted on PubMed using the MeSH terms: hepatic encephalopathy; minimal hepatic encephalopathy; overt hepatic encephalopathy; covert hepatic encephalopathy; definition; classification; diagnosis; quality of life; pathophysiology; cirrhosis; neurophysiological tests; psychometric tests; management; rifaximin; screening.

Pathogenesis

Pathogenesis of hepatic encephalopathy is complex: hyperammonaemia plays a key role. Inflammation and pro-inflammatory cytokines, altered neurotransmission, false neurotransmitter generation and oxidative stress are implicated. The liver normally metabolizes gut toxins, such as ammonia, at first pass. With development of hepatocellular failure and portal-systemic shunting, toxins reach the systemic circulation, and eventually the brain (Bleibel et al, 2012).

Hyperammonaemia and an inflammatory response work synergistically, affecting cerebral function (Ferenci et al, 2002). Astrocytes are the only cerebral cells metabolizing ammonia; their adaptive response is the cellular basis of most changes in hepatic encephalopathy (Haussinger et al, 2000). Astrocytes convert ammonia into glutamine, changing cellular osmolality, drawing in water, causing astrocyte swelling and potentiating cerebral oedema (Cash et al, 2010). Raised intracellular levels of ammonia lead to altered neurotransmission. These alterations to astrocytes and oxidative stress are closely linked in an 'auto-amplifying' loop (McPhail et al, 2010). The gut microbiome generates additional neurotoxic molecules, such as phenols, mercaptans and short-chain fatty acids, which enhance the toxic effects of ammonia. However, doubts have been cast on the central role of ammonia. Its concentration in the blood does not correlate with levels in the CSF or with severity of symptoms, therefore hyperammonaemia is more likely one of a multitude of factors contributing to the development of hepatic encephalopathy (Bismuth et al, 2011).

Owing to the altered haemodynamic mechanisms in cirrhosis and portosystemic shunting, a chronic state of endotoxaemia is present (Bleibel and Al-Osaimi, 2012). In response, astrocytes and microglial cells release cytokines such as tumour necrosis factor (TNF) and interleukin-1-beta (IL-1β). TNF compromises the endothelial blood–brain barrier and IL-1β affects integrity of the glial side of the blood–brain barrier. These both act to increase blood–brain barrier permeability and can increase cerebral diffusion of ammonia (Ferenci et al, 2002).

Other theories centre on altered neurotransmission

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter. Patients with hepatic encephalopathy have elevated levels of GABA as a result of incomplete catabolism by the liver. Similarly, increased levels of endogenous benzodiazepines are present, which bind to the GABA–benzodiazepine receptor complex, increasing neuroinhibition (Bismuth et al, 2011).

Explanations for the genesis of hepatic encephalopathy come in and out of fashion, depending on the weight of evidence. Another older theory for this multifactorial condition is derived from animal models and concerns the development of false neurotransmitters, such as octopamine and phenylethanolamine, which may bind to adrenergic receptors. Aromatic amino acids are precursors for these false neurotransmitters, which exhibit very weak adrenergic activity. Hepatocellular failure may lead to a reduced ability to metabolize aromatic amino acids in the liver and increased delivery to the brain, potentially causing reduced sympathetic drive and contributing to the impaired cognition seen in hepatic encephalopathy (Capocaccia et al, 1984; Hilgier et al, 1985).

Zinc, which facilitates excretion of ammonia, may be depleted in cirrhosis, potentiating the harmful effects of ammonia, while accumulation of manganese in the basal ganglia of patients who have cirrhosis has also been noted (Cash et al, 2010).

Diagnosis

Diagnosis of hepatic encephalopathy can be difficult. Unrelated neurological and/or metabolic causes of encephalopathy, such as alcohol withdrawal, subdural haematomas, CNS sepsis, ketoacidosis and hypoxia, must be excluded. Liver function tests, blood glucose, blood gases and serum electrolytes, computed tomography, magnetic resonance imaging and electroencephalography can be used to help differentiate from other CNS diseases (Kato et al, 2008; Bleibel and Al-Osaimi, 2012).

Arterial, venous and/or capillary ammonia levels are commonly measured in patients who are suspected to have overt hepatic encephalopathy, as facilities for this are

widely available. Hyperammonaemia is associated with the development of hepatic encephalopathy (Mardini and Record, 2012). However, ammonia levels do not necessarily correlate with the severity of symptoms relating to hepatic encephalopathy, so the clinical context must always be considered (Bismuth et al, 2011; Tapper et al, 2015).

Minimal hepatic encephalopathy must be diagnosed using sensitive neuropsychological and neurophysiological tests when there is no clinical evidence of hepatic encephalopathy (Kato et al, 2008). No consensus has been established regarding the specific tests required, but the negative socioeconomic impact and association with poor health-related quality of life indicate the need for a diagnostic 'gold standard'. The subtle presentation of the disorder raises questions as to whether only patients who have noticeable changes in daily functioning (work performance, difficulty in concentration, changes in behaviour) should be tested (Stewart and Smith, 2007). It is sensible to ask patients questions related to health-related quality of life, changes in behaviour and changes in mental status, as well as to perform quantitative neuropsychometric and neurophysiological tests (Kato et al, 2008). The various diagnostic tests and their respective advantages and disadvantages are outlined in *Table 2*. An example of a pencil-and-paper neuropsychometric test is shown in *Figure 1*.

Despite being designed to detect cognitive changes associated with minimal hepatic encephalopathy, neuropsychometric tests are often insensitive; they may also be influenced by variables such as age, educational status and learning ability. Consideration must also be given to the medical history and each patient's clinical context to avoid misdiagnosis as a result of these potential confounders (Prakash and Mullen, 2010; Vilstrup et al, 2014). Many tests are time-consuming or require specialized personnel for their administration. These barriers result in a lack of standardized testing to diagnose minimal hepatic encephalopathy. Further research and debate are required to determine a 'gold standard' for real-world clinical practice; a test that can be easily implemented and validated could substantially change minimal hepatic encephalopathy diagnosis (Prakash et al, 2013). On the other hand, neurophysiological tests such as critical flicker frequency provide more objective results (Kircheis et al, 2002; Sharma et al, 2007).

Treatment

Health-care providers have traditionally focused on managing overt hepatic encephalopathy, with treatment of minimal hepatic encephalopathy a preserve of the research field (Prakash et al, 2013). Management goals when treating overt hepatic encephalopathy are as follows:

Table 2. Advantages and disadvantages of diagnostic tests for hepatic encephalopathy

Diagnostic test		Advantages	Disadvantages
Serum levels of ammonia		Can correlate with severity of hepatic encephalopathy	Not reliable enough to inform diagnosis or management
Clinical criteria for overt hepatic encephalopathy	West Haven criteria	Well-established, large evidence base	Inter-observer variation (especially in low grades of hepatic encephalopathy)
	Hepatic encephalopathy scoring algorithm (HESA)	Good reproducibility, can characterize low-grade hepatic encephalopathy	Time consuming
Neuropsychometric tests ('paper and pencil' tests) for minimal hepatic encephalopathy	Psychometric hepatic encephalopathy score (PHES)	Diagnosis of subtle cognitive changes	Poor test of memory, difficulty interpreting score. Reliance on measuring fine motor skills
	Repeatable Battery for the Assessment of Neurological Status (RBANS)	Quicker than other tests	Can be difficult to interpret
Computerized psychometric tests for minimal hepatic encephalopathy	Inhibitory control test	High sensitivity, reliable when compared to others	Time consuming, difficult instructions to understand
	Cognitive Drug Research (CDR) system	Correlates well with neuropsychometric tests	Time consuming
Neurophysiological tests	Critical flicker frequency	High sensitivity and specificity, correlates well with neuropsychometric tests	Not widely available
	Electroencephalography	Detects hepatic encephalopathy via slow frequency electrical activity	Variable sensitivity for the diagnosis of hepatic encephalopathy
Brain imaging	Magnetic resonance imaging	Many modalities and techniques available, can identify several abnormalities caused by hepatic encephalopathy	Expensive, some metal products (certain types of pacemaker, aneurysm clips) not allowed
	Computed tomography	Easily excludes other causes of encephalopathy	Poor sensitivity for low-grade cerebral oedema, radiation exposure

From Prakash and Mullen (2010)

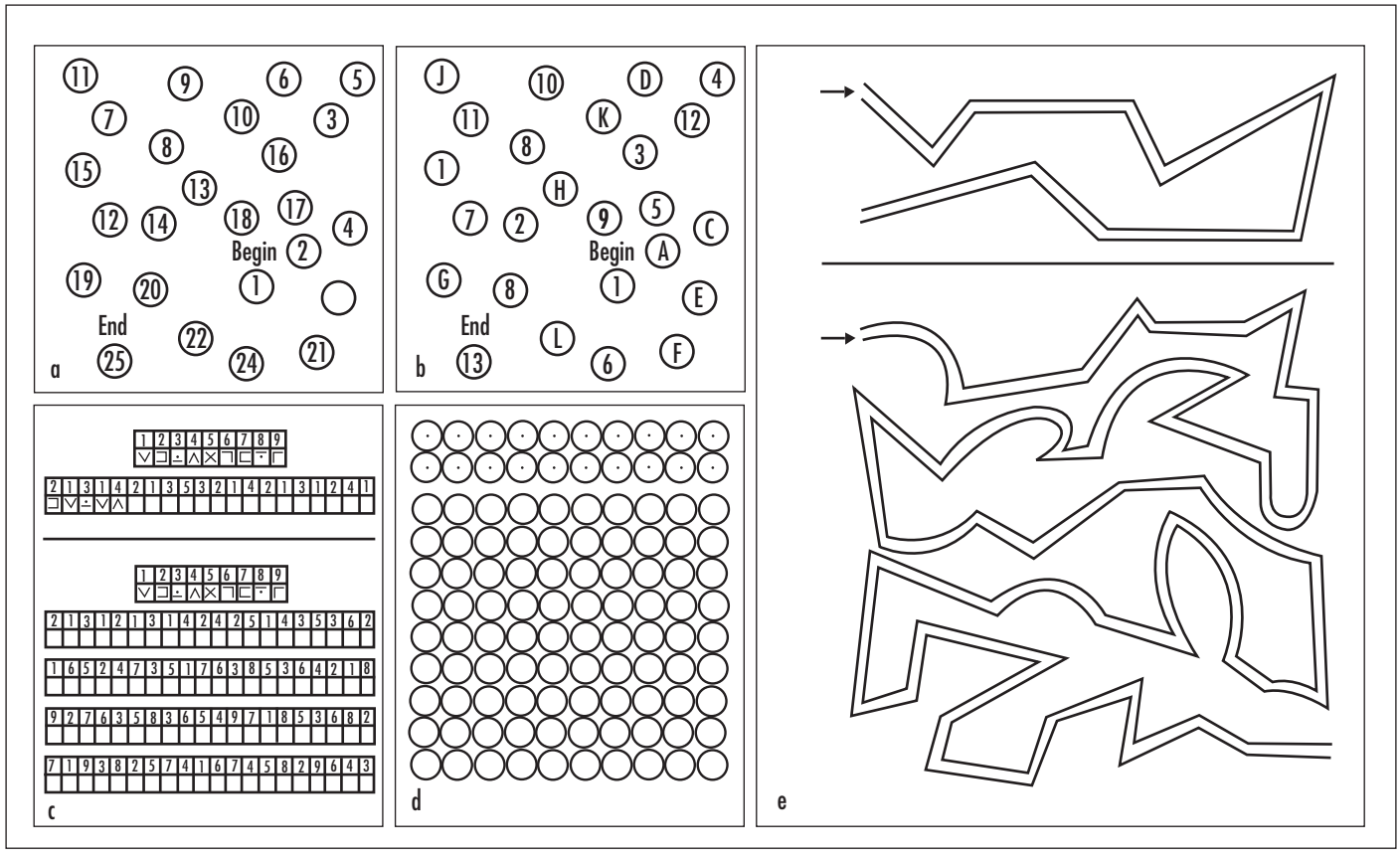

Figure 1. The paper-and-pencil tests that make up the Psychometric Hepatic Encephalopathy Score (PHES) assessing attention, visual perception and visuo-constructive abilities. a. Number connection test-A. b. Number connection test-B. c. Digit-symbol test. d. Serial dotting. e. Line drawing.

1. Provision of supportive care
2. Identification and removal of precipitating factors
3. Reduction of nitrogenous load from the gut
4. Assessment of need for long-term therapy.

Precipitating factors, such as gastrointestinal haemorrhage, infection, electrolyte disturbances, renal dysfunction, use of psychoactive drugs, constipation and acute liver failure, must be investigated and dealt with appropriately (Blei et al, 2001). Treatments largely focus on removal of bacteria-derived toxins and modulating gut flora levels. Probiotics, non-absorbable disaccharides and antibiotics can be effective in improving hepatic encephalopathy (Prakash et al, 2013).

Non-absorbable disaccharides include lactulose and lactitol, which are well known for their laxative effects; they also reduce the colonic pH and decrease mucosal uptake of glutamine in the gut (van Leeuwen et al, 1988). This reduces synthesis and absorption of ammonia. Lactulose is the first-line therapy for acute episodic overt hepatic encephalopathy with a meta-analysis performed in 2004 suggesting that non-absorbable disaccharides were superior to placebo, but did not improve overall survival. However, when the authors only considered high-quality trials, no effect on hepatic encephalopathy was found (Als-Nielsen et al, 2004). Despite some conflicting results, lactulose has been used effectively for years to reverse episodic overt hepatic encephalopathy in all but the most severe cases. This discordance between the literature and clinical efficacy may arise from heterogeneity in types of hepatic encephalopathy and subjectivity of assessment tools (Leise et al, 2014). Adherence issues are a problem with this treatment, as patient self-titration is required to achieve 2–3 bowel movements per day, with common side effects of diarrhoea, flatulence and abdominal cramps (Prakash et al, 2013). Kalaitzakis et al (2006) found that daily lactulose use negatively correlated with health-related quality of life in 128 patients with cirrhosis ($r= -0.27$, $P<0.01$) and independently correlated with gastrointestinal symptom severity ($ß = 0.65$, $P<0.01$).

Rifaximin is a minimally-absorbed oral antibiotic with few adverse effects, no reported drug–drug interactions and a low risk of inducing bacterial resistance (Vilstrup et al, 2014). A phase 3 multicentre study found that remission of hepatic encephalopathy was prolonged in patients treated with rifaximin. It had a protective effect, reducing hospitalization rates (Bass et al, 2010). Rifaximin has therefore been approved by the Food and Drug Administration for secondary prevention of overt hepatic encephalopathy. This has been greeted with great enthusiasm and widely used in the USA, although some trials have shown no difference in hepatic encephalopathy grade improvement or other end-points between rifaximin and lactulose treatment (Mullen et al, 2007).

In the UK, the National Institute for Health and Care Excellence (2015) now recommends rifaximin as a first-line treatment for secondary prevention of hepatic encephalopathy, citing a more favourable side-effect profile compared to lactulose. However, the American and European guidelines do not recommend its use as monotherapy or in primary prophylaxis (Vilstrup et al, 2014). Given the limited evidence available, as a result of the small number of trials and methodological imperfections, the use of rifaximin as monotherapy for episodic overt hepatic encephalopathy remains contentious.

Alteration of gut flora with probiotics, prebiotics or synbiotics improves hepatic encephalopathy by lowering blood ammonia concentrations (Bleibel and Al-Osaimi, 2012). The compound salt L-ornithine-L-aspartate works by providing substrates for the urea cycle and stimulating glutamine synthesis in skeletal muscle, decreasing ammonia concentration (Leise et al, 2014). It has been evaluated in chronic hepatic encephalopathy, and has been shown to improve hepatic encephalopathy grade when used as adjunctive treatment to standard medical treatment. One study showed patients with grade 2 hepatic encephalopathy or above had a significant (P=0.019) improvement in hepatic encephalopathy grade on standard medical treatment and L-ornithine-L-aspartate (79%), compared to standard medical treatment and placebo (55%) (Abid et al, 2011).

Intravenous branched-chain amino acids have also been shown to be effective in a meta-analysis. Patients with cirrhosis receiving branched-chain amino acids were more likely to recover from hepatic encephalopathy than those who did not (Muto et al, 2005). They act as a source of glutamate, increasing metabolism of ammonia in skeletal muscle (Leise et al, 2014). Other studies reveal mixed results, with high cost and limited availability of branched-chain amino acid preparations, suggesting this treatment should only be considered in severely protein-intolerant patients (Bleibel and Al-Osaimi, 2012). In fact, branched-chain amino acids are rarely used in clinical practice outside east Asia.

Alongside branched-chain amino acid supplementation, high-protein or protein-unrestricted diets are also recommended, as cirrhosis results in a catabolic state. Vegetable-based protein is recommended because its high fibre content increases intestinal transit time, colonic motility and enhances intestinal nitrogen clearance (Amodio et al, 2001). Certain oral, poorly absorbed antibiotics such as neomycin, vancomycin and metronidazole have been used in some countries to reduce ammonia-producing enteric bacteria for lactulose-intolerant patients. However, use of these agents has declined around the world as a result of the risk of antibiotic resistance, systemic absorption and associated adverse effects, with reports of ototoxicity and nephrotoxicity with neomycin and paromomycin, peripheral neuropathy and gastrointestinal disturbances with metronidazole and vancomycin (Prakash et al, 2013).

Treatment of minimal hepatic encephalopathy

Research on minimal hepatic encephalopathy treatment is evolving, but similarly to treatment of overt hepatic encephalopathy, little evidence exists to support just one therapy. The clinical significance of minimal hepatic encephalopathy is its impact on the patient's health-related quality of life, driving skills and of the risk of progression to overt hepatic encephalopathy. Of course, overt hepatic encephalopathy exhibits significant impairment of health-related quality of life, but the relationship between health-related quality of life and minimal hepatic encephalopathy is not as well supported. One study showed minimal hepatic encephalopathy detected in 43% of the cirrhosis patients tested, but only one out of eight domains in the Short Form 36 Health Survey (physical functioning) was significantly different compared to a control group (Kircheis et al, 2009). Minimal hepatic encephalopathy is associated with significant impairment in daily functioning, such as in social interaction, alertness, sleep quality, work and recreation, compared to patients with cirrhosis but without minimal hepatic encephalopathy (Prasad et al, 2007). Additionally, the inability to work has profound socioeconomic implications, particularly in jobs requiring the use of fine motor skills, such as handling machinery (Schomerus and Hamster, 2001; Stewart and Smith, 2007).

The impact on driving ability has been widely assessed, as minimal hepatic encephalopathy exerts negative effects on attention, psychomotor function and working memory, all of which are essential for driving (Ortiz et al, 2005). A study using a driving simulator found that about 44% of patients with minimal hepatic encephalopathy were unfit to drive, with similar findings demonstrated by others (Watanabe et al, 1995). Minimal hepatic encephalopathy may therefore increase the risk of accidents. Assessment of fitness to drive itself requires specialized consultation and no standard rules exist on how this should be performed (Ortiz et al, 2005). Finally, patients with minimal hepatic encephalopathy may improve, remain unchanged or develop overt hepatic encephalopathy over a long-term follow-up. Minimal hepatic encephalopathy and survival requires further investigation to establish a stronger association, but the probability of overt hepatic encephalopathy at 3 years is 56% for those with minimal hepatic encephalopathy and 8% for those without (Hartmann et al, 2000).

Ethical considerations

Alongside issues concerning which diagnostic test to use and which treatment to give is the question of whom to test for minimal hepatic encephalopathy. Some authors suggest all patients with cirrhosis should be tested to identify those with minimal hepatic encephalopathy (Quero Guillén et al, 2002; Stewart and Smith, 2007). The rationale for this catch-all approach is that therapy may improve quality of life and delay development of

overt hepatic encephalopathy. Screening all patients would also allow identification of patients who are at risk when driving motor vehicles and operating complex machinery, decreasing the risk to the patient and to society (Stewart and Smith, 2007). Conversely, others suggest that as minimal hepatic encephalopathy is asymptomatic or causes few symptoms, treatment benefits on quality of life are probably small (van Leeuwen et al, 1988), while subjecting patients to potential side effects of treatment. Lack of a 'gold standard' test and the controversial nature of treatment available discourage screening of all patients with cirrhosis. Therefore, the decision to test for minimal hepatic encephalopathy should be individualized and dependent on the extent to which the diagnosis and subsequent treatment could modify or improve the quality of life of a particular patient.

In fact, assuming treating the condition will improve the health-related quality of life of patients is controversial. Some studies prove amelioration of minimal hepatic encephalopathy, therefore some authors encourage providing therapy for all patients. However, the significant side effects may mean the benefits of therapy are reduced, especially in patients with minimal hepatic encephalopathy. This dilemma introduces ethical implications to the management of hepatic encephalopathy. A 'trial of therapy' may be useful if the patient is amenable to this. A final consideration is to the use of prophylactic therapy for patients with cirrhosis. Given the favourable tolerability and safety profile of rifaximin and its use reducing the recurrence of overt hepatic encephalopathy, it has been suggested as an ideal candidate for minimal hepatic encephalopathy prophylaxis in patients with cirrhosis. Although it cannot be endorsed at this time, minimal hepatic encephalopathy prophylaxis with rifaximin warrants future research (Prakash et al, 2013).

KEY POINTS

- Hepatic encephalopathy is a neuropsychiatric condition resulting from hepatocellular failure and/or portosystemic shunting. It can be graded using the West Haven or SONIC criteria.
- Hyperammonaemia and neuroinflammation are the main mechanisms leading to astrocyte swelling and the cerebral decline seen in hepatic encephalopathy.
- Diagnosis and assessment of hepatic encephalopathy can be performed using computer-based or paper-and pencil neuropsychometric tests, or neurophysiological tests such as an electroencephalogram.
- Treatments for overt hepatic encephalopathy can reverse an acute episode and are effective in preventing deteriorations in at-risk patients. Reducing the nitrogenous load received from the gut is the main mechanism by which treatment works.
- Minimal hepatic encephalopathy is very common in cirrhosis patients and has negative effects on a patient's quality of life, particularly the ability to drive. However, more work is needed to assess its relationship to mortality.
- Screening for and treating minimal hepatic encephalopathy is contentious and further work needs to be done to observe its viability. The ethics of treating seemingly asymptomatic patients must be considered.

Conclusions

There are many unanswered questions concerning the exact pathogenesis, detection, quantification and effective treatment of hepatic encephalopathy. The effects of infection, inflammation and chronic cerebral oedema and their significance in the progression of hepatic encephalopathy are still being elucidated. There is a lack of consensus in choosing a 'best' diagnostic test to detect hepatic encephalopathy, which can lead to disparities in the best time to intervene with therapy. Owing to the negative implications of the condition for the patient's quality of life, productivity and prediction of the development of overt hepatic encephalopathy, management of minimal hepatic encephalopathy is an important concern (Stewart and Smith, 2007). Additionally, with the safety and legal issues associated with driving performance and potential cost of road traffic accidents, interest in proactive diagnosis and management of minimal hepatic encephalopathy in the clinical practice setting is increasing (Prakash et al, 2013).

With hepatic encephalopathy eventually occurring in up to 50% of patients with cirrhosis, as well as an associated poor prognosis, it is important to test patients to offer them the available therapeutic options. Benefits of treatment should be weighed against any negative effects on quality of life. The use of rifaximin as adjunctive therapy to lactulose for severe overt hepatic encephalopathy is supported by research, as is its use in prevention of recurrent hepatic encephalopathy. It is recommended that patients with minimal hepatic encephalopathy are counselled about the risks of driving in addition to undergoing a fitness-to-drive evaluation in the outpatient setting (Leise et al, 2014). For minimal hepatic encephalopathy, further research is required to determine the conditions under which the benefits of testing and the following treatment outweigh the costs, both economical and societal. **BJHM**

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