Hepatic encephalopathy

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Abstract

Hepatic encephalopathy (HE) is a neurocognitive disorder associated with both acute and chronic liver injury. It manifests as a wide spectrum of neuropsychological abnormalities ranging from subtle impairments in executive higher functions through to coma. In acute liver failure, the central role of ammonia in the development of brain oedema remains undisputed. However, the gut microbiome and the presence of systemic inflammation or the development of infection have become increasingly recognized as drivers for developing HE in cirrhosis. The development of HE is often unpredictable and its management, particularly in a ward environment, remains challenging. Patients frequently require augmented levels of care in a high-dependency or intensive care area. The probability of maintaining a transplant-free survival after a first episode of HE at 3 years is only 23%, so referral for liver transplantation should be considered early. This review covers the practical aspects of managing HE and provides an up-to-date overview of the evidence base in this area, focusing predominantly on its management in chronic liver disease.

Keywords Ammonia; antibiotics; brain oedema; gut microbiome; hepatic encephalopathy; infection; inflammation; lactulose; MRCP; precipitating factor; rifaximin

Key points

- Overt hepatic encephalopathy (HE) in a patient with chronic liver disease portends a poor prognosis, and early referral for transplantation should be considered
- HE is debilitating and is associated with a poor quality of life
- Patients should be advised not to drive
- Identification and reversal of precipitating factors is key to managing the acutely encephalopathic patient
- Reversal of dehydration, correction of hyponatraemia and treatment of infection are particularly important
- For patients with grade 3/4 HE, early admission to a high-dependency/intensive care environment for airway support should be sought
- In acute liver failure, early referral to a tertiary liver centre is mandatory
- Do not neglect nutrition; nasogastric feeding is often required to ensure nutritional requirements are being met

Introduction

Hepatic encephalopathy (HE) encapsulates a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction, after excluding other known brain disease. It remains a major clinical problem in patients with cirrhosis and is the feature that defines prognosis in acute liver failure. HE is divided into two components: overt and minimal (covert) HE. Overt HE can be diagnosed clinically through a pattern of symptoms and signs, whereas minimal HE can require specialized psychometric or neurophysiological testing, although it can be evident from a thorough history from the patient and their caregiver.[1]

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In acute liver failure, patients can develop significant brain swelling; increased intracranial pressure complicates 25% of cases of acute and hyperacute, and 9% of subacute, liver failure. In cirrhosis, HE causes a range of neuropsychiatric disturbances spanning from stupor and coma to subtle abnormalities in higher executive function apparent only when psychometric tests are performed. It has been estimated that the annual risk of developing overt HE with cirrhosis is 20%, and 60–80% of cirrhotic patients have evidence of minimal (covert) HE on testing.

Definitions

The heterogeneous nature of the presentation of HE (Table 1) has made the interpretation of comparative studies problematic. This has led to the development of consensus terminology to classify HE (Table 2).

Clinical staging

The staging of overt HE remains an imprecise art that is often hampered by its fluctuant course. The West Haven criteria are perhaps the best-known scoring system, with the severity of HE being graded from 0 to 4 (Table 3). When the level of consciousness is impaired in patients with more severe grades of HE, the Glasgow Coma Scale score can offer a more objective assessment (Table 3).

Classification of HE[1]

Type	Definition
A (Acute)	Acute and hyperacute liver failure
B (Bypass)	Portosystemic bypass without intrinsic hepatocellular disease
C (Cirrhosis)	Cirrhosis and portal hypertension with portosystemic shunts

Table 1

Clinical presentation of HE[1]

Encephalopathy	Definition
Acute	Acute liver dysfunction
Recurrent or episodic	Episodes of mental alteration in a patient with cirrhosis even in the absence of a known precipitating factor
Persistent	Neurological deficit that persists despite the reversal of liver injury, e.g. after transplantation or the removal of a precipitating factor
Minimal or covert (previously known as subclinical)	No evidence of overt encephalopathy but subtle cognitive deficits may be detected with a neuropsychological function test battery

Table 2

Pathogenesis

In the presence of liver injury, urea synthesis is impaired and the brain acts as an alternative ammonia detoxification pathway. Astrocytes have the ability to eliminate ammonia by synthesizing glutamine. Hyperammonaemia leads to the accumulation of glutamine within astrocytes, which exerts an osmotic stress causing the astrocytes to take in water and swell. In acute liver failure, astrocytes swell and patients develop cytotoxic brain oedema.

This has also been elegantly demonstrated, using magnetic resonance imaging (MRI), in patients with minimal HE undergoing liver transplantation. A decrease in magnetization ratio indicative of increased brain water was correlated with abnormalities in neuropsychological function and was reversed by liver transplantation.

There is growing recognition of the gut microbiome playing a pivotal role in the pathogenesis of HE, with the development of salivary and gut dysbiosis and a reduction in bacterial diversity with replacement of healthy gut commensals by potentially pathogenic species. This is accompanied by an increase in gut permeability and small bowel bacterial overgrowth, which culminates in bacterial translocation, endotoxaemia and dysregulated immune activity.

Infection is a frequent precipitant of HE and studies have demonstrated a rapid progression in the severity of HE in patients with acute liver failure who have more marked inflammation. These observations have been confirmed in patients with cirrhosis.[2]

Diagnosis

History and examination

Establishing a diagnosis of HE requires a history or clinical evidence of liver disease. A thorough history and clinical examination are essential; the differential diagnosis includes intracranial events, electrolyte abnormalities and sepsis. During assessment the presence of a precipitating factor such as gastrointestinal bleeding or infection must be sought. Reversal of the sleep–wake cycle, poor concentration and short-term memory loss can suggest minimal HE.

Evaluation and simultaneous management of the airway and vital observations should be performed at the outset. Asterixis is defined as a flapping tremor; care should be taken not to confuse this with alcohol withdrawal or intoxication. Hyperreflexia can also be present. If a focal neurological deficit is elicited, an alternative diagnosis to HE must be considered. Clonus can frequently be elicited in patients with grade 3/4 HE.

Investigations

Laboratory tests

Routine blood biochemistry and glucose should be checked as part of the initial assessment. Diagnostic tests should be directed

Clinical scoring of HE

Grade using the West Haven criteria[3]	Clinical features	Glasgow Coma Scale score
0	No abnormality apparent on clinical examination	15
1	Short-term memory loss, difficulty in concentrating and reversal of the sleep–wake cycle	15
2	Lethargy, apathy, drowsiness, flapping tremor (asterixis), disorientation, confusion, inappropriate behaviour	12–15 (verbal response or obeying command typically impaired)
3	Stuporose but easily rousable, marked confusion, incoherent speech	6–12
4	Coma, unresponsiveness	3–6 (may respond to painful stimuli)

Table 3

towards identifying a precipitant, such as gastrointestinal bleeding, infection or electrolyte disturbance. If there is clinically detectable ascites, a diagnostic tap on admission is mandatory to exclude spontaneous bacterial peritonitis; this can be confirmed by the presence of a polymorphonuclear count of at least 250/mm^3 in the ascitic fluid. Urine and blood cultures should also be taken as part of a full septic screen. An isolated elevated arterial ammonia concentration can help to confirm the diagnosis of HE; however, a normal or mildly elevated blood ammonia does not exclude a diagnosis of HE, even in patients presenting with a reduced level of consciousness.

Imaging

Computed tomography (CT) of the head is often required to exclude an alternative cause of the altered level of consciousness, especially when the history is limited. In acute liver failure, CT can reveal features of raised intracranial pressure, but patients are frequently too sick to be moved from intensive care. In low-grade HE, no diagnostic features are discernible on CT, but it can be helpful in excluding an intracranial bleed in patients with thrombocytopenia and coagulopathy.

Brain MRI can be a helpful diagnostic tool as it can rule out the presence of hippocampal atrophy in Alzheimer's disease or small vessel changes associated with vascular dementia. A liver ultrasound scan can exclude the development of hepatic/portal vein thrombosis and hepatocellular carcinoma. Vascular-phase abdominal CT has a role in excluding large spontaneous portosystemic shunts.

Neuropsychological tests

In clinical practice, the use of the seven-pointed star and 'serial 7s' test can be helpful at the bedside to detect neurocognitive dysfunction in cirrhotic patients with suspected low-grade HE. The animal naming test is quick and easy to do in clinical settings. Naming 15 animals in 1 minute produced the best discrimination between unimpaired and minimal/grade 1 HE patients.

The recently published HE in chronic liver disease guidelines by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) provides a comprehensive list of the neurophysiological and psychometric tests used. These should be performed by experienced examiners and be used for individuals who will benefit most from testing, such as those with impaired quality of life or implications for employment or public safety.[3]

Electroencephalography (EEG)

Triphasic waves may be seen on the EEG in patients with advanced HE. However, EEG is a relatively insensitive diagnostic test in patients with minimal (covert) or low-grade HE. Some centres can perform visual, somatosensory or auditory evoked potentials that may offer greater sensitivity, but these lack robust validation.

Management

Precipitating factors

The overarching priority in any patient with cirrhosis presenting with HE is to actively seek out and treat any precipitating factor(s) (Table 4).

Infection: a low threshold for antibiotic use in this population should be adopted. Sepsis and/or the systemic inflammatory response syndrome occurs in approximately 40% of hospitalized patients with cirrhosis, and the resultant organ failures lead to significant mortality. If a septic focus is found, local antibiotic policy should be consulted. However, in the absence of positive microbial cultures an empirical prompt 3–5-day course of a broad-spectrum antibiotic is prudent, such as piperacillin –tazobactam 4.5 g three times daily intravenously or as per local microbiology guidelines.

Gastrointestinal bleeding: an upper gastrointestinal bleed results in a significant ammonia load that frequently leads to the development of HE. Evidence-based guidelines support the use of an empirical 5-day course of antibiotic in any patient who presents with variceal bleeding, especially where there is a risk of aspiration pneumonia.

Constipation: enemas can be used in the acute setting and often rapidly improve conscious level. Evidence for the use of lactulose in acute HE is limited (see below); in the outpatient setting, it should be used with the aim of producing two bowel movements per day. Lactulose can produce bloating and flatulence, which can lead to poor compliance; the development of diarrhoea and dehydration can paradoxically increase, rather than reduce, the risk of developing HE.

Electrolyte disturbance: electrolyte abnormalities should be corrected. Hyponatraemia commonly results in HE and is often rectified by withholding diuretic therapy and avoiding the use of glucose 5%. Volume expansion with 1 litre of intravenous normal saline increases renal ammonia excretion and is an effective treatment for acute HE but is frequently underused. In severe (grade 3/4) HE, haemofiltration efficiently reduces blood ammonia concentration, especially in individuals with renal dysfunction.

Specific interventions

The majority of HE treatments are directed towards the gut as the principal ammonia-producing organ. UK patients diagnosed with overt or minimal (covert) HE should inform the Driver and Vehicle Licensing Agency and are advised not to drive.

Non-absorbable disaccharides: for 35 years, lactulose has been the first-line drug treatment in HE. A systematic review of 22 trials of lactulose for acute HE concluded that there was

Precipitating factors of HE

- Infection
- Ammonia load (e.g. upper gastrointestinal bleed, portocaval shunt)
- Dehydration
- Hyponatraemia
- Electrolyte imbalance/metabolic disarray
- Constipation
- Sedatives/opiate analgesics (e.g. benzodiazepines)

Table 4

insufficient high-quality evidence to recommend its use. No large multicentre placebo-controlled trial has ever been performed. In patients who have already presented with overt HE; however, an open-label, single-site study demonstrated that, compared with placebo, lactulose was effective in preventing overt HE for up to 20 months.[4]

Rifaximin: this is a non-absorbable antibiotic that was approved in Europe and the USA after a randomized, double-blind, placebo-controlled trial of 299 patients. This demonstrated that, over a 6-month period, treatment with rifaximin maintained remission from HE more effectively than placebo and significantly reduced the risk of hospitalization with HE.[5] The National Institute for Health and Care Excellence recommends it as an option for reducing recurrent episodes of overt HE. The EASL/AASLD guidelines state that rifaximin is an effective add-on therapy to lactulose for preventing overt recurrences of HE.

L-Ornithine L-aspartate (LOLA): oral or intravenous LOLA can be used as an alternative or additional agent to treat patients with advanced HE not responding to conventional therapy; however, it is not licensed in the UK.

Nutrition

Weight loss and sarcopenia can worsen HE. Low-protein nutrition should be avoided in these patients, and care should be taken to ensure that adequate protein and energy intake is maintained.

Liver transplantation

The probability of transplant-free survival after a first episode of HE in cirrhosis is only 42% at 1 year and 23% at 3 years, so consideration for referral for liver transplantation should be made early.

Acute liver failure

Acute liver failure is a life-threatening, multisystem illness resulting from massive liver injury. Early identification of these patients and referral to centres experienced in the management of acute liver failure are essential. In patients with established HE, strategies to prevent the onset of severe cerebral oedema and intracranial hypertension aim to maintain freedom from sepsis and adequate sedation, reduce cerebral blood flow and avoid hypo-osmolality. Survival has been transformed by emergency liver transplantation, which is now part of routine care for patients with who meet criteria indicative of a poor prognosis. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 57-year-old man presented with confusion and incontinence of urine. He had previously been found to have alcohol-related cirrhosis. But had been abstinent from alcohol for 7 months.
On clinical examination, he had a Glasgow Coma Scale score of 15/15 but was poorly orientated and could not remember his grandchildren's names. He had a flapping tremor and a moderate volume of ascites.

What is the most appropriate next step in his management?

A. Give 1 litre of 5% dextrose over 4 hours intravenously
B. Give 40 ml of lactulose to drink
C. Perform an acute infection screen
D. Place him on a low-protein diet
E. Request an urgent CT of the brain

Question 2

A 68-year-old man presented with a complaint of frequently nodding off during the day and difficulty sleeping at night. He could no longer do the crossword that he easily used to complete. He picks his grandchildren up from school in the car. He had previously been found to have non-alcoholic steatohepatitis and cirrhosis.

What would be the most appropriate next step in his management?

A. Advise him not to drive, and inform the Driver and Vehicle Licensing Agency
B. Check the blood ammonia level
C. Commence oral lactulose 15 ml twice daily with the aim of passing two or three soft stools per day
D. Refer him to the dementia clinic
E. Undertake a neuropsychological test battery

Question 3

A 28-year-old woman was reviewed after a second admission for acute overt hepatic encephalopathy (HE). She was now alert and orientated. She had previously been found to have autoimmune hepatitis and cirrhosis. She was taking lactulose 10 ml 12-hourly and had just completed a 5-day course of empirical antibiotic therapy for a mild chest infection.

What would be the most important next step in her management going forwards?

A. Request a contrast CT scan to look for spontaneous shunts
B. Advise rifaximin, which, in conjunction with lactulose, will reduce the likelihood of HE recurring
C. Discontinue immunosuppressant therapy to reduce the risk of infection
D. Advise oral L-ornithine L-aspartate (LOLA)
E. Refer for urgent assessment for liver transplantation