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 subclinical alterations to coma. In acute liver failure, the central role of ammonia in the development of brain oedema remains undisputed. However, the roles of inflammation, infection and the gut microbiota have become increasingly recognized as factors modulating the cerebral impact of hyperammonaemia 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 arena. The probability of maintaining a transplant-free survival after a first episode of HE at 3 years is only 23% and therefore 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, focussing predominantly on the management of the condition in chronic liver disease.

Keywords ammonia; antibiotics; brain oedema; hepatic encephalopathy; infection; inflammation; lactulose; precipitating factor; rifaximin

What's new?

- The growing awareness of the synergistic role of inflammation, infection and ammonia has led to widespread use of antibiotics as a first-line treatment in hepatic encephalopathy (HE)
- Rifaximin is the first drug for over 30 years to receive US Food and Drug Administration approval for the treatment of HE. It has now been licensed in the UK and received NICE approval for the secondary prevention of HE in March 2015 [NICE Technology Appraisal: TA337]. Trials are underway to further clarify the mechanisms of action of this drug and the role of the gut microbiota in the generation of systemic inflammation and oxidative stress
- The inter-organ metabolism of ammonia has also become a focus for therapeutic development and hepatologists are increasingly thinking 'outside the colon'. Clinical studies on metabolic ammonia scavengers are underway, and may widen the therapeutic armamentarium for these patients

Introduction

Hepatic encephalopathy (HE) describes the spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction, after exclusion of other known brain disease.[1] 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 HE and minimal (covert) HE. Overt HE can be diagnosed clinically through a pattern of symptoms and signs, whereas minimal HE requires specialized psychometric or neurophysiologic testing.

In acute liver failure, patients may develop significant brain swelling; increased intracranial pressure complicates 25% of acute and hyperacute, and 9% of subacute liver failure cases.[2] In cirrhosis, HE causes a range of neuropsychiatric disturbances spanning from stupor and coma to subtle abnormalities 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 may have evidence of minimal (covert) HE on testing.[3]

Definitions

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

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.[4] When the level of consciousness is impaired in those patients with more severe grades of HE, the Glasgow coma score may offer a more objective assessment (Table 3).

Pathogenesis

In the presence of liver dysfunction, urea synthesis is impaired and the brain acts as an alternative ammonia detoxification pathway. Astrocytes have the ability to eliminate ammonia by the synthesis of glutamine, through amidation of glutamate by the enzyme glutamine synthetase. 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.[5] 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 correlated with abnormalities in neuropsychological function and was reversed by liver transplantation.[6]

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Competing interest: none declared.

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Classification of hepatic encephalopathy[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

Cerebral hyperaemia is also critical in the development of intracranial hypertension in acute liver failure.[7] 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.[8] These observations have been confirmed in patients with cirrhosis.[9,10]

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.

An 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 may 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 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, which can be confirmed by the presence of an ascitic fluid polymorphonuclear count of at least 250/mm^3. Urine and blood cultures should also be taken as part of a full septic screen. An isolated elevated arterial ammonia concentration may help to confirm the diagnosis of HE but a normal or mildly elevated blood ammonia does not exclude a diagnosis of HE,[11] even in patients presenting with a reduced level of consciousness.[10]

Clinical presentation of hepatic encephalopathy[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 such as following 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

Clinical scoring of hepatic encephalopathy

Grade using West Haven criteria[4]	Clinical features	Glasgow coma score
0	No abnormality apparent on clinical examination	15
1	Short-term memory loss, difficulty in concentrating and reverse of 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, unresponsive	3–6 (may respond to painful stimuli)

Table 3

Imaging

A computed tomography (CT) scan 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 may reveal features of raised intracranial pressure but patients are frequently too sick to be moved from the intensive care unit. 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. A liver ultrasound scan will exclude the development of hepatic/portal vein thrombosis and hepatocellular carcinoma. Vascular phase abdominal CT has a role in excluding large spontaneous portosystemic shunts. MRI and positron emission tomography (PET) are used predominantly in the research setting.[3]

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. Several tests are available to evaluate neurocognitive impairment in cirrhosis; the use of these is confined predominantly to the diagnosis of minimal HE.[3] The recently published HE in