Hepatic Encephalopathy

Introduction

Hepatic encephalopathy (HE) is a common complication of decompensated cirrhosis. It presents with a broad spectrum of potentially reversible neuropsychiatric abnormalities, ranging from subclinical or covert hepatic encephalopathy (CHE) to clinically apparent or overt hepatic encephalopathy (OHE) [1]. Studies suggest that up to 70% of patients with cirrhosis will experience HE at some point during the course of their disease.

Following the diagnosis of HE, overall survival is approximately 2 years regardless of etiology, and approximately 1 year in patients older than 65 years [1]. HE is also associated with increased hospitalizations and healthcare costs, as well as reduced quality of life for both patients and caregivers.

Although treatment for HE is effective when used appropriately, little progress has been made over the past 30 years. In addition, treatment guidelines are not consistently followed by many physicians.

HE in patients with chronic liver disease is potentially reversible and treatable. However, HE associated with rapidly rising blood ammonia levels is more difficult to control because of diffuse cerebral edema and structural brainstem injury [2].

Suspected Hepatic Encephalopathy

At diagnosis, 10% to 14% of patients with compensated cirrhosis and 16% to 21% of those with decompensated cirrhosis have overt hepatic encephalopathy (OHE) [1]. Following placement of a portosystemic shunt, 10% to 50% of patients are at risk of developing OHE. Early recognition and prompt treatment of HE are essential for improving outcomes.

HE may present in a variety of ways, ranging from subtle and difficult-to-detect manifestations to severe confusion or coma in patients with advanced liver disease [1]. Covert hepatic encephalopathy (CHE) affects a substantial proportion of patients with cirrhosis, although they may appear well during a routine consultation. These patients are prone to occupational difficulties, motor vehicle accidents, and falls. A significant number will progress to OHE. Therefore, patients with advanced liver disease, whether or not they have a history of HE, should be assessed for HE at every clinical encounter.

Early signs of HE may be subtle, such as forgetfulness and irritability, which patients themselves may not recognize. Simple questions or a dedicated assessment instrument may be used to

evaluate cognitive status [3]. Caregivers can play an important role in screening by identifying symptoms such as forgetfulness, insomnia, word-finding difficulties, changes in driving ability, difficulties with simple calculations, or personality changes (e.g., irritability).

Diagnosis

The diagnosis of OHE is based on clinical examination [3]. The West Haven criteria are the preferred diagnostic standard. However, they are subjective and demonstrate limited interobserver reliability, especially for Grade I disease, although the detection of disorientation and asterixis shows good reliability.

Diagnosing cognitive dysfunction itself is not difficult, as it can be established through clinical observation or formal testing. The challenge lies in attributing the dysfunction to HE [3]. For this reason, OHE remains a diagnosis of exclusion in a patient population susceptible to mental status changes caused by medications, alcohol misuse, recreational drug use, hyponatremia, and psychiatric disorders. Therefore, when clinically indicated, alternative causes should be excluded through laboratory and/or radiological evaluation in patients presenting with altered mental status.

West Haven Criteria [3]

Grade	Category	Description	Operational Criteria
Normal	No impairment	No HE and no history of HE	Normal test results
Minimal	CHE	Abnormal psychometric or neuropsychological testing without clinical manifestations of mental status changes	-
Grade I	CHE	Mild lack of awareness; euphoria or anxiety; shortened attention span; impaired addition or subtraction; altered sleep rhythm	Despite being oriented in time and space, the patient appears to have cognitive or behavioral deterioration compared with their usual baseline as judged clinically or by caregivers
Grade II	OHE	Lethargy or apathy; disorientation in time; obvious personality change; inappropriate behavior; dyspraxia; asterixis	Disorientation in time; at least 3 of the following are incorrect: day of month, day of week, month, season, or year ± other symptoms
Grade III	OHE	Somnolence or semi-stupor; responsive to stimuli; confusion; marked disorientation; bizarre behavior	Disorientation also in place; at least 3 of the following are incorrect: country, region, city, or location ± other symptoms
Grade IV	OHE	Coma	No response even to painful stimuli

The abnormalities must be attributable to liver failure or a portosystemic shunt.

Elevated blood ammonia levels alone do not provide additional diagnostic, staging, or prognostic value in HE among patients with chronic liver disease. However, if ammonia is measured in a patient with OHE and the level is normal, the diagnosis of OHE becomes questionable [3]. For ammonia-lowering therapies, repeated measurements may be useful to assess treatment efficacy.

Several factors may precipitate episodic or recurrent OHE [3].

Precipitating Factors

Episodic	Recurrent
Infections	Electrolyte disturbances
Gastrointestinal bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disturbances	Constipation
Constipation	Diuretic overdose
Unidentified	Gastrointestinal bleeding

(Frequency decreases from top to bottom.)

Among precipitating factors, infections deserve particular attention. Both infections and hyponatremia may independently cause encephalopathy and may also precipitate HE through interaction with underlying pathophysiological mechanisms.

Differential Diagnosis

The differential diagnosis of HE includes multiple conditions [3]:

- OHE or acute confusional state
  - Diabetes-related disorders: hypoglycemia, ketoacidosis, hyperosmolar state, lactic acidosis
  - Alcohol-related disorders: intoxication, withdrawal, Wernicke-Korsakoff syndrome
  - Drug-induced states: benzodiazepines, antipsychotics, opioids
  - Electrolyte disturbances: hyponatremia, hypercalcemia
  - Non-convulsive status epilepticus
  - Psychiatric disorders
  - Intracranial hemorrhage and stroke
  - Severe systemic illness with organ failure and inflammation
- Other presentations
  - Dementia
  - Structural brain lesions, including trauma, neoplasms, and normal-pressure hydrocephalus
  - Obstructive sleep apnea

Wernicke-Korsakoff syndrome, particularly the amnestic state of Korsakoff syndrome, may mimic HE [2]. A confusional state shares many features of early HE, including inattention, reduced awareness, irrational answers to questions, and tangentiality. Confabulation may occur in early Korsakoff syndrome, but a short-term or anterograde amnestic syndrome with inability to retain words, names, or tasks is invariably present.

Features of acute alcohol-withdrawal delirium overlap with those of worsening HE. However, alcohol-withdrawal delirium is characterized by coarse rhythmic tremor, shouting, slurred speech, and autonomic dysfunction with cold sweats, features not typically observed in HE [2]. Neurological findings are generally non-specific.

Recent metabolic disturbances may reduce responsiveness and occur with dilutional hyponatremia, hypoglycemia, and metabolic alkalosis. Their effects on HE are usually modest because they are generally transient. A substantial reduction in serum sodium is required to cause impaired responsiveness or seizures [2]. Conversely, overly rapid correction of serum sodium may result in central pontine myelinolysis, particularly in patients with alcoholic hepatitis or cirrhosis.

Non-convulsive status epilepticus is a difficult diagnosis and requires expertise in electroencephalographic interpretation.

Acute or chronic subdural hematoma may mimic HE, although focal neurological signs are often present on examination. Alcohol use disorder and chronic liver disease increase the risk of subdural hematoma but not the risk of intracranial hemorrhage.

Treatment

Episodes of OHE are treated with specific medications, including non-absorbable disaccharides such as lactulose and antibiotics such as rifaximin [3]. In hospitalized patients who are unable to swallow, a nasogastric tube may be inserted.

Routine treatment of minimal HE and CHE is not recommended and should be considered on a case-by-case basis.

Particular attention should be given to precipitating factors such as infections, gastrointestinal bleeding, dehydration, and hyponatremia. These factors should be corrected whenever possible.

Lactulose

Lactulose is generally used as first-line therapy for OHE. Failure to respond to lactulose should prompt a rapid search for unrecognized precipitating factors and alternative causes of cerebral dysfunction [3]. Lactulose should be initiated at 25 mL every 1 to 2 hours until at least two soft or loose bowel movements are produced daily. The dose should then be titrated to maintain two to three bowel movements per day. Excessive use carries risks including aspiration, dehydration, hypernatremia, and severe perianal skin irritation. Overuse may itself precipitate HE.

Rifaximin

Rifaximin is indicated to reduce the risk of recurrent OHE [4]. It is administered at a dose of 550 mg twice daily and may be used in combination with lactulose. In one study, patients receiving rifaximin plus lactulose had a lower incidence of spontaneous bacterial peritonitis and urinary tract infections with sepsis compared with those receiving lactulose alone.

Prophylaxis

Any patient with cirrhosis and a history of HE should be discharged with prophylactic therapy to reduce the risk of recurrent HE and hospital readmission [4]. Following the initial episode of HE, lactulose is recommended for secondary prevention. After a second episode, rifaximin should be added to lactulose to prevent further recurrences [3]. Routine prophylaxis to prevent HE following transjugular intrahepatic portosystemic shunt (TIPS) placement is not recommended.

In principle, prophylaxis against recurrent HE is continued indefinitely. However, if precipitating factors are well controlled, such as infections or esophageal variceal bleeding, or if there is improvement in liver function or nutritional status, prophylaxis may be discontinued.

References

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