Hepatic Encephalopathy
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Hepatic encephalopathy (HE) is a syndrome of neuropsychiatric dysfunction caused by portosystemic venous shunting, with or without intrinsic liver disease [1]. Patients with HE often present with the onset of mental status changes ranging from subtle psychologic abnormalities to profound coma. Several hypotheses have been proposed to explain the mental impairment associated with portosystemic shunting and liver disease. Clinicians diagnosing HE frequently have the opportunity to intervene and reverse severe HE, even hepatic coma. The recent advances in understanding and management of HE are the subject of this article.

Epidemiology and clinical significance

HE is a common complication of advanced cirrhosis. Between one third to one half of hospitalizations for cirrhosis are related to HE [2]. The frequency of hospitalization for HE has nearly doubled over the last decade, with lengths of stay between 5 and 7 days [2]. Patients with HE often have other manifestations of end-stage liver disease, such as ascites, jaundice, or gastrointestinal variceal bleeding. HE can also develop as an isolated manifestation of decompensated cirrhosis. HE usually signals advanced liver failure, and is often considered a clinical indication for evaluation for liver transplantation [3]. HE may disable the patient from employment, driving, and self-care, and require involvement of family or household members in the care of affected patients. The clinical importance of HE is underscored by the frequent reversibility of the precipitating factors.
Risk factors

Severe, acute, or chronic liver disease and portosystemic venous shunting are the sine qua non for the development of HE. The more advanced the liver disease, the more likely the development of HE. Patients with cirrhosis who have minimal HE (formerly known as “subclinical” HE) are at risk of developing overt HE [4]. Placement of a transjugular intrahepatic portosystemic shunt (TIPS) is also a risk factor. Patients who have diabetes mellitus or malnutrition seem to develop HE more frequently with cirrhosis [5]. HE is an essential component of acute liver failure [6]. Severe hyperammonemia (> 150–200 μmol/L) with acute liver failure can cause cerebral edema that contributes to HE [7]. Patients with portal vein thrombosis and extensive portosystemic shunting without significant parenchymal liver disease occasionally develop HE. Other risk factors can precipitate HE (Box 1).

Types of hepatic encephalopathy

HE is clinically classified into three major categories, according to the underlying hepatic condition (Table 1) [8]. Type A occurs in patients with acute liver failure. Type B occurs in patients without intrinsic liver disease but with large, noncirrhotic, portosystemic shunting. Type C is related to underlying cirrhosis with portosystemic shunting. Type C is the most common form. It can be episodic or persistent. Episodic HE can lead to repeated hospitalizations, often caused by precipitating factors (see Box 1). The HE

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**Box 1. Precipitating factors for hepatic encephalopathy**

- Dehydration
- Gastrointestinal bleeding
- Infections (especially spontaneous bacterial peritonitis, urinary tract, skin, or pulmonary)
- Constipation
- Excessive dietary protein
- Central nervous system acting drugs
- Hypokalemia
- Renal failure
- Urinary obstruction
- Hyponatremia
- Surgery
- Transjugular intrahepatic portal-systemic shunt
- Superimposed liver injury (acute hepatitis, drug-induced liver injury)
- Hepatocellular carcinoma
- Terminal liver disease
episode can be treated by correction of precipitating factors (see later). Sometimes an episode of HE may not have recognizable precipitating factors (spontaneous episodic HE). Some patients develop recurrent HE. If the HE lasts beyond 4 weeks or is recurrent, type C HE is considered “persistent.” Both episodic and persistent HE can be adequately suppressed by therapy, but may reappear after therapy discontinuation.

Clinical presentation

HE presents with a broad spectrum of clinical manifestations (Table 2). The patient or household contacts may describe changes in mentation, such as a decrease in memory and concentration ability, mental fogginess, or mild confusion. With severe manifestations, a patient may rapidly

Table 1
Types of hepatic encephalopathy

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Type A</td>
<td>Encephalopathy from acute liver failure</td>
</tr>
<tr>
<td>Type B</td>
<td>Encephalopathy caused by portosystemic shunting, without intrinsic liver disease</td>
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<tr>
<td>Type C</td>
<td>Encephalopathy of cirrhosis associated with portosystemic shunting: Episodic: precipitated, spontaneous, or recurrent</td>
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<th>Table 2</th>
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<tr>
<th>Encephalopathy</th>
<th>Consciousness</th>
<th>Intellectual function</th>
<th>Personality behavior</th>
<th>Neuromuscular abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (mild)</td>
<td>Abnormal sleep pattern</td>
<td>Shortened attention span, mildly impaired computations</td>
<td>Euphoria, depression, irritability</td>
<td>Metabolic tremor, muscular incoordination, impaired handwriting</td>
</tr>
<tr>
<td>Stage II (moderate)</td>
<td>Lethargy, mild disorientation</td>
<td>Amnesia, grossly impaired computations</td>
<td>Overt change in personality, inappropriate behavior</td>
<td>Slurred speech, asterix (flapping), hypoactive reflexes, ataxia</td>
</tr>
<tr>
<td>Stage III (severe)</td>
<td>Somnolence, semistupor</td>
<td>Inability to compute</td>
<td>Paranoia, bizarre behavior</td>
<td>Hyperactive reflexes, nystagmus, Babinski’s sign, clonus, rigidity</td>
</tr>
<tr>
<td>Stage IV (coma)</td>
<td>Stupor, unconscious</td>
<td>None</td>
<td>None</td>
<td>Dilated pupils, opisthotonus, coma</td>
</tr>
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</table>

develop overt mental changes, such as grossly inappropriate behavior, slurred speech, and marked personality changes that can progressively deteriorate into a stuporous, comatose state. This can lead to urgent hospitalization for evaluation of suspected stroke or drug overdose. Seizures are an uncommon manifestation of HE. The patient developing HE is typically unaware of the changes in behavior, personality, and consciousness. An encephalopathic patient may resist evaluation and have to be managed in accordance to his or her lack of competency if grossly confused, inappropriate, or agitated. Conn and Lieberthal [1] proposed a thorough clinical assessment of HE (see Table 2). Ortiz and colleagues [9] recently evaluated a nine-item linear scale to assess HE severity, but this scale is relatively complex and contains components that often develop asynchronously. A practical and simple gradation of HE is commonly used clinically, but entails significant subjective observer bias (Table 3) [1]. The presence of a flapping tremor (asterixis) signifies stage II. The flapping often weakens as HE progresses to stage III and disappears in stage IV. The complex portosystemic encephalopathy index is an arbitrary composite score designed to assess HE severity [1]. This index grades the level of abnormality of arterial blood ammonia level, electroencephalogram, asterixis, mental state, and trail-making test time. It is a valuable research tool for clinical trials, particularly to evaluate therapeutic agents, but is too complex for standard clinical practice. An objective, relatively simple, specific, and sensitive method to diagnose and assess the severity of HE has not yet been devised. The patient history often yields clues of underlying liver disease, whether chronic viral hepatitis C or B, autoimmune liver disease, fatty liver, or alcoholic liver disease. In any patient presenting with mental changes and prior liver disease, HE is a major element in the differential diagnosis that requires investigation. The patient with HE may have had a recent precipitating event, such as gastrointestinal bleeding, spontaneous bacterial peritonitis, other infections, dehydration, constipation, excessive dietary protein intake, excessive alcohol intake, urinary obstruction, and electrolytic derangements (see Box 1). Physical examination may reveal a disheveled appearance or

<table>
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<tr>
<th>Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No abnormality detected</td>
</tr>
<tr>
<td>1</td>
<td>Shortened attention span, impaired addition and subtraction skills, mild euphoria or anxiety</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy, apathy, disoriented to time, personality change, inappropriate behavior</td>
</tr>
<tr>
<td>3</td>
<td>Somnolence, semistupor, responsive to stimuli, confused when awake, gross disorientation</td>
</tr>
<tr>
<td>4</td>
<td>Coma, little or no response to stimuli, mental state not testable</td>
</tr>
</tbody>
</table>

other signs of inadequate self-care. The mental status examination discloses signs ranging from confusion and disorientation (stage II); to somnolence (stage III); to unresponsive coma (stage IV) (see Table 3). Physical findings can help grade the severity of encephalopathy. Asterixis is absent in stage I, and present in stage II, but may become difficult to elicit and weak in stage III. The asterixis and other signs can be intermittent, wax and wane, or inconsistently occur in patients with a given stage of HE. Generally, the neurologic examination in HE demonstrates nonlocalizing signs of diffuse neuropsychologic dysfunction, as in other metabolic encephalopathies. Focal neurologic signs are occasionally present, such as nystagmus, Babinski’s sign, clonus, opisthotonus, and even decerebrate and decorticate posturing in stage IV. In a prospective study, 17.4% of HE episodes exhibited focal neurologic signs [10]. Hemiplegia and hemiparesis were the most common focal neurologic signs, but hemiagnosia and monoplegia were also observed [10]. Seizures were more common in patients with focal neurologic signs. The focal neurologic deficits resolved, without sequelae, in parallel with the resolution of the HE [3]. The development of focal neurologic signs or seizures in a patient with encephalopathy should lead to appropriate brain imaging, however, because structural brain lesions, such as subdural hematomas, can cause the focal neurologic signs.

Differential diagnosis and evaluation

HE may clinically mimic other entities, including other metabolic toxic-encephalopathies, transient ischemic attack, stroke, intracranial hemorrhage, brain tumors, and brain abscesses (Box 2). A thorough diagnostic evaluation is required to exclude these alternative diagnoses to establish

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**Box 2. Major differential diagnoses in hepatic encephalopathy**

- Metabolic encephalopathies caused by uremia, sepsis, hypoxia, hypoglycemia, ketoacidosis, hypercapnea, thyroid dysfunction, or cerebral edema
- Intracranial bleeding: subdural hematoma, intracranial hemorrhage
- Ischemic brain disease: transient ischemic attack, ischemic stroke
- Central nervous system abscess, encephalitis, meningitis (bacterial, viral, fungal)
- Central nervous system neoplasm
- Delirium tremens
- Alcoholism
- Postictal state
the diagnosis of HE. An evaluation for other causes of abnormal mental status is necessary even in patients with recurrent episodes of severe HE (stage ≥II). Multiple causes of encephalopathy may be identified, such as HE and uremic encephalopathy in a patient with liver failure and hepatorenal syndrome. Cerebral edema or even fatal uncal herniation have rarely been described in cirrhotic patients with HE [11–13].

History and physical examination are key tools in diagnosing overt HE. An elevated blood ammonia level and absence of structural lesions on brain imaging support the diagnosis. The previously reported discrepancy between blood ammonia levels and HE severity was related to problems with the biochemical assay for ammonia. Ammonia is a labile compound. Spontaneous deamination and evaporation at room temperature during storage may occur. These factors can cause errors in blood ammonia results. If properly processed, blood ammonia levels correlate well with the severity of HE [14–17]. Furthermore, venous blood ammonia level, when properly assayed, correlates well with arterial ammonia level [13]. When evaluating a patient with mental status changes, blood ammonia levels should be drawn in a nonheparinized container, immediately placed on ice, and assayed within 30 minutes. Normal blood ammonia levels in a patient with severe mental status changes do not support the diagnosis of HE. Conversely, an elevated ammonia level in a comatose patient does not exclude coexistent conditions contributing to the abnormal mental status (see Box 2). Markedly elevated ammonia levels in a comatose patient (>150–200 μmol/l), however, are strongly suspicious of HE, provided there is no history of recent seizures. Blood ammonia levels may be moderately elevated in patients with cirrhosis without HE.

Head CT or MRI is important to exclude structural lesions as causes of an abnormal mental status. Even though the electroencephalogram may demonstrate the triphasic spikes frequently seen in HE, the test is not routinely used to diagnose HE. Electroencephalogram is useful when the diagnosis is uncertain, such as in the presence of focal neurologic signs or seizure activity, or in a comatose patient. Psychometric tests, such as the Number Connection Test or other variants of simple computational chores, can help document the clinical course of HE and assess response to therapy of patients with stage I or II HE. These tests lack specificity because they can reflect other forms of toxic-metabolic encephalopathy. More complex neurophysiologic and neuropsychologic tests used to diagnose minimal (subclinical) forms of HE are unnecessary to evaluate patients with overt HE. Minimal HE frequently precedes the development of overt HE.

**Pathogenesis**

Ultimately, HE results from functional disturbances of cells involved in neurotransmission. The neurologic impairment in HE is believed to be caused by multiple factors (Fig. 1). Previous hypotheses had attempted to
explain HE by individual neurotoxic mediators or disruption of single neurotransmitters [17–25]. Several mechanisms, however, likely induce the observed abnormalities of neuronal and astrocytic function. Potential pathogenic factors include a direct neurotoxic effect of ammonia, oxidative stress caused by generation of reactive oxygen species, endogenous benzodiazepine-like ligands, subclinical intracellular astrocytic edema, γ-aminobutyric acid–like molecules that act as γ-aminobutyric acid agonists, abnormal histamine and serotonin neurotransmission, endogenous opiates, neurosteroids, inflammatory cytokines, and potential manganese toxicity [17,18,26]. Hyperammonemia is directly neurotoxic and may also sensitize astrocytes and neurons to injury by other pathways and mediators [27]. Further research is needed to ascertain the therapeutic implications of these multiple pathways for HE.

**Precipitating factors**

Precipitating factors are critically important in the diagnosis and management of HE. They are responsible for most episodes of HE. They should be diligently sought in patients with liver disease presenting with mental status changes. HE without apparent precipitating factors from terminal cirrhosis is uncommon. Episodic HE should be attributed to liver failure only after systematically excluding all the precipitating factors (see Box 1).

The mechanisms by which precipitating factors induce HE are diverse and incompletely understood. When encephalopathy is associated with gastrointestinal bleeding or dietary protein overload, excessive ammonia precursors (amino acids, peptides, and proteins) cause increased ammonia production [28,29]. This may lead to neuronal and astrocyte dysfunction. Increased intake of dietary protein may not be readily apparent or volunteered by the encephalopathic patient. This information should be sought from household members. Other precipitating factors (hypoxia, hypovolemia, excessive amounts of central nervous system–acting drugs, antidepressants, sedatives, analgesics, and severe hyponatremia) likely operate by direct neuronal inhibition. Even at standard dosages, central nervous system–acting

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**Fig. 1.** Neurologic impairment factors in HE.
agents may accumulate in patients with advanced cirrhosis because of decreased hepatic clearance. Elevated serum drug levels can cause mental status changes. Hypokalemic alkalosis potently stimulates renal ammoniagenesis. Renal dysfunction, including the hepatorenal syndrome, may decrease renal ammonia excretion. A hypercatabolic state induced by septic complications, such as spontaneous bacterial peritonitis or other infections, provides increased precursors for ammonia synthesis that may directly inhibit neuronal function by cytokines or endotoxins. Finally, increased portosystemic venous blood shunting caused by hepatocellular carcinoma or intercurrent portal vein thrombosis may increase the delivery of ammonia and other neurotoxins to the central nervous system.

Treatment

Proper management of HE requires identification and treatment of the precipitating factors (see Box 1). This treatment is probably more potent than any pharmacotherapy. Multiple precipitating factors are often present. An episode of HE should be attributed to end-stage cirrhosis only after careful exclusion of the known precipitating factors. Similarly, the diagnosis of HE in a patient with underlying liver disease is established only after excluding other etiologies for mental status changes.

Correction of precipitating factors

Dehydration, from excessive diuresis, diarrhea, or vomiting, is a common and easily correctable precipitating factor. Patients with severe ascites may be intravascularly depleted and dehydrated. Clinical signs of dehydration, and elevated serum creatinine and other laboratory tests consistent with hemoconcentration, establish the diagnosis. Dehydration is reversed by discontinuation of diuretics, intravenous infusion of physiologic saline, and therapy for the underlying cause of increased fluid and electrolyte losses. Gastrointestinal bleeding is identified and treated appropriately. Microorganisms cultured from infected sites (spontaneous bacterial peritonitis, urinary tract infection, pneumonia, cellulitis, and so forth) should be diagnosed and treated with appropriate antibiotics. Broad-spectrum antibiotics should be initiated after obtaining pancellures when infection is suspected in patients with stage III or IV HE, such as in patients with fever or unexplained leukocytosis. The onset of HE requires diagnostic paracentesis in a patient with ascites, for analysis of cell type, cell count, Gram stain, and culture. Hypokalemia should be vigorously corrected with parenteral potassium in HE. Severe hyponatremia (serum sodium <125 mEq/L) can contribute to HE, particularly when the sodium level is less than 120 mEq/L. Discontinuation of diuretics and appropriate free-water restriction are required. Limited infusions of hypertonic saline (3% NaCl, 150 mL intravenous) may be
needed for very severe hyponatremia. The new vasopressin receptor antagonists have shown promising results in treating severe hyponatremia with cirrhosis. They can be considered for patients with severe HE and severe hyponatremia [30–32]. HE precipitated by excessive dietary protein intake or use of sedatives often gradually resolves provided that the patient receives general supportive care and specific pharmacologic therapy for HE (see next). Urinary obstruction by prostatic processes, genitourinary stones, or renal insufficiency, including the hepatorenal syndrome, should be treated. Pulmonary infections, acute respiratory distress syndrome, large pleural effusions, sleep apnea, and other forms of respiratory insufficiency causing hypoxemia should be appropriately treated in the setting of HE. Pharmacologic therapy with lactulose or nonabsorbable antibiotics should be undertaken or intensified in patients with HE who are being weaned from mechanical ventilation.

**Pharmacologic therapy**

Agents that induce diarrhea or modulate intestinal bacterial flora can decrease ammonia production and increase ammonia excretion. The commonly used agents include lactulose, lactitol, neomycin, rifaximin, and metronidazole [17,18,33–36].

**Lactulose**

For many years, lactulose was the only pharmacologic agent available to treat HE [1,35,37–50]. This nonabsorbable disaccharide is administered orally at initial dosages of 30 mL two to four times daily. This therapy should induce mild diarrhea, with three to five semisolid bowel movements daily. Some patients achieve this goal with small dosages, whereas others require large amounts of lactulose. Oral lactulose is helpful for the outpatient who requires maintenance therapy for chronic or recurrent HE, and for the inpatient with episodic HE. In this latter instance, lactulose is used in conjunction with correction of the precipitating factors. Lactulose is administered orally to patients with stage I or II encephalopathy. Oral administration may be hazardous in patients with stage III or IV HE because of the risk of pulmonary aspiration. In patients with severely depressed consciousness, lactulose is administered by a nasogastric tube. Lactulose cannot be given orally in patients with suspected ileus, and is inadvisable in patients with tense ascites. Patients with advanced HE are preferably administered lactulose by colonic retention enemas (300 mL of lactulose plus 700 mL of tap water) [45]. The amount of lactulose administered by enemas is much greater than that administered orally or by nasogastric tube. Administration by enemas causes less abdominal distention because of avoidance of lactulose passage through the small bowel. Lactulose enemas may be preferable for the patient who has stage III or IV encephalopathy, severe ascites, spontaneous bacterial peritonitis, or is otherwise unable to have
a nasogastric tube inserted. Some patients cannot retain the enemas for a sufficient time because of incontinence.

Lactulose therapy has significant limitations, including a very sweet taste, increased intestinal gas production, abdominal distention and cramping, and diarrhea [48,49]. These adverse events are common and often lead to poor compliance in outpatients. Patients may skip dosages or take lactulose sporadically. Inadequate compliance is the major limitation of lactulose therapy.

**Oral antibiotics**

Inhibition of production of ammonia or other neurotoxins by intestinal bacteria has promoted the use of antibiotics, such as neomycin, metronidazole, vancomycin, and rifaximin [37,40,41,50–56]. The evidence for efficacy of neomycin is ambiguous [50], however, and it entails some toxicity. Metronidazole and oral vancomycin have been studied to a very limited extent. Rifaximin, a nonabsorbable rifamycin antibiotic derivative, has been found to be effective therapy in numerous clinical trials [52,54,55,57–64]. It lacks significant toxicity and side effects because of minimal gastrointestinal absorption. Rifaximin has gained rapid acceptance as either first-line or as adjunct therapy to lactulose. It has been evaluated primarily in comparison with lactulose, but is often clinically used in combination with lactulose. The number and length of hospitalizations for HE was significantly reduced after treatment with rifaximin, compared with lactulose-treated patients in two retrospective American studies [54,55]. A dose-effect study suggested that 1200 mg/day of rifaximin was superior to lower doses, but the difference was marginal [61]. Rifaximin at somewhat lower doses is currently under prospective evaluation in a large United States multicenter trial.

**Dietary protein**

Restriction of dietary protein to 40 g/day or less used to be advocated for patients with HE because excessive dietary protein can precipitate HE. Prolonged protein restriction in HE, however, can exacerbate the catabolic state of cirrhosis and cause release of amino acids and other nitrogenated by-products from muscles. The current recommended protein diet for patients with a history of HE is 0.8 to 1.5 g/kg/d. Patients admitted for a bout of stage III–IV HE often have low protein intake for the first several days of hospitalization, primarily related to an inability to ingest meals. As soon as possible, they should resume a normal protein content in their diet by either oral or enteral feedings [65]. Patients with chronic HE occasionally do not tolerate normal amounts of dietary protein. A switch to vegetable protein [66] or supplementation with branched-chain amino acids may be considered in this situation [16,17]. Branched-chain amino acid preparations are relatively expensive.
Artificial liver support

Devices to temporarily replace critical hepatic functions could be useful for HE. In irreversible acute or chronic liver failure, a liver-assist device could stabilize the patient until a suitable liver donor becomes available for urgent liver transplantation. The device could sustain a patient with HE while correcting the precipitating factors. Several devices have been analyzed during the last few decades. A bioartificial liver, consisting of cartridges packed with porcine hepatocytes, was recently evaluated for acute liver failure [67]. This trial demonstrated no benefits in survival or in the neurologic status [67]. A large, multicenter, randomized controlled trial compared the molecular absorbent recirculating system (MARS), a variant of extracorporeal albumin dialysis, plus standard medical therapy (lactulose plus neomycin or metronidazole) for 5 days versus standard medical therapy alone in patients with stage III or IV HE [68]. MARS therapy produced significantly more rapid and frequent improvement in HE, but the study was not blinded [68]. Other trials have shown discrepant effects of MARS on survival in acute-on-chronic liver disease. Given the complexity and cost of MARS, more evaluation is necessary before this modality can be clinically advocated. New artificial support systems, such as the selective plasma hemofiltration, have shown promising preliminary results in HE and are undergoing large clinical trials [69].

Chronic therapy

Patients with persistent or chronic HE should be carefully evaluated for persistent or intermittent, low-grade gastrointestinal bleeding, including bleeding from portal hypertensive gastropathy or colopathy. Frequent dietary ingestion of more than 1.5 g/kg of protein per day may cause persistent or chronic HE. Consultation with a dietician for dietary evaluation and counseling concerning the limits and types of dietary protein intake, is necessary in HE patients. Without identifiable precipitating factors, persistent HE related to deteriorating liver function or after TIPS may require chronic therapy with lactulose or the nonabsorbable antibiotic rifaximin to suppress HE. The modest effects of lactulose therapy on HE were first described several decades ago [1,35,37–50]. Long-term compliance with lactulose is poor, and patients often take it intermittently. Lactulose and nonabsorbable antibiotics act synergistically, and the combination may permit reducing the dosages of each agent. Chronic antibiotic administration can lead to bacterial resistance, bacterial overgrowth, and fungal colonization. It is unknown whether chronic therapy with nonabsorbable antibiotics for persistent or chronic HE should be continuous or cyclic to minimize the potential for resistance or fungal overgrowth [59]. Chronic neomycin administration can cause otovestibular toxicity because of the small, but significant, gastrointestinal absorption of this aminoglycoside.
Hepatic encephalopathy, cerebral edema, and increased intracranial pressure in liver failure

Patients with cirrhosis and HE rarely develop cerebral edema that leads to elevated intracranial pressure. A few case reports have described cerebral edema in cirrhosis [11,12], but a review of the data suggests that other causes for cerebral edema, such as hypoxic injury or seizures, had not been completely excluded. Autopsy studies in patients who expired from complications of cirrhosis, including HE, rarely show significant cerebral edema. Conversely, cerebral edema is a common finding at autopsy of patients who died from acute liver failure (formerly known as “fulminant hepatitis”). Nevertheless, studies using sensitive techniques, such as MRI spectroscopy, have reported increased water content in the cirrhotic brain [13]. This finding suggests that subclinical neuronal or astrocytic edema could have a pathogenic role in chronic HE. The current evidence does not support placement of intracranial pressure transducers in cirrhotic patients who develop HE. The situation is different in patients with acute (fulminant) liver failure who develop stage III or IV HE. Given the high frequency of significant cerebral edema in this setting, with an attendant risk of uncal herniation, these patients are candidates for the placement of an intracranial pressure transducer [6]. An intracranial pressure transducer is often required to diagnose intracranial hypertension because a head CT scan is relatively insensitive to detection of early cerebral edema in acute liver failure [70].

If the initial intracranial pressure reading is normal, the encephalopathy could be ascribed to metabolic encephalopathy of liver failure (HE), and therapy should be directed at lowering the serum ammonia level. If, however, the opening intracranial pressure is greater than 10 mm Hg, the hepatic coma may be caused by the cerebral edema. In this situation, the therapy consists primarily of mannitol, mild hypothermia, and barbiturate infusion in refractory cases [6]. Ammonia seems to play a role in swelling of astrocytes by incorporation into glutamine [17,18,20], but vascular reactivity, cerebral perfusion, and other humoral factors are also important in the pathogenesis of intracranial hypertension in fulminant hepatitis. The identification of the role of hyperammonemia in the intracranial hypertension of acute liver failure has provided a rationale for administration of ammonia-lowering therapy, including lactulose or nonabsorbable antibiotics in this setting. The latter agents are preferred because lactulose may produce large amounts of gas in the small bowel, which can cause difficulties with abdominal closure during liver transplantation.

Hepatic encephalopathy after transjugular intrahepatic porto-systemic shunt

The introduction of TIPS represented a major advance in the management of refractory ascites or esophagogastric variceal hemorrhage
unresponsive to pharmacologic or endoscopic therapy [71–73]. From 20% to 77% of patients receiving TIPS develop HE, with the rate of HE dependent on the patient’s residual liver function [71–73]. The severity of HE after TIPS is variable and ranges from HE easily controlled with antibiotics or disaccharides to chronic HE that is refractory to combination therapy. In general, stage II or higher HE is a contraindication to TIPS therapy. Occasionally, however, TIPS must be performed as life-saving therapy for indications, such as uncontrollable variceal bleeding, regardless of a history of HE.

TIPS is also increasingly performed for ascites refractory to diuretics [71,72]. A recent large meta-analysis found that TIPS may, in fact, be superior to large-volume paracentesis [74]. TIPS is certainly not urgent for ascites, and paracentesis often offers a reasonable alternative therapy. A history of stage II or higher HE constitutes a relative contraindication for TIPS therapy for ascites. Insertion of TIPS in patients with Child-Pugh class C cirrhosis can lead to further hepatic decompensation, resulting in acute liver failure, severe HE, and even cerebral swelling [12]. Clinical trials of TIPS for ascites generally excluded patients with Child-Pugh class C with total serum bilirubin level $> 5$ mg/dL, or with stage II or higher HE. These criteria should also be used in clinical practice. Salerno and colleagues [74] recently showed that the following features independently predicted onset of HE after TIPS: age greater than 60 years; low mean arterial blood pressure; high MELD score; and a low post-TIPS porto-systemic pressure gradient (from a widely open stent). These factors must, therefore, be considered when contemplating TIPS installation for refractory ascites.

Prophylactic therapy with lactulose or antibiotics after insertion of TIPS is not recommended except for a patient prone to HE who has been rescued from uncontrollable variceal hemorrhage by urgent TIPS [75]. Patients may experience a few episodes of HE within the first few months after TIPS. Standard therapy with nonabsorbable antibiotics (with or without lactulose) often produces a satisfactory outcome. Intentional narrowing or therapeutic occlusion of the TIPS stent rarely becomes necessary when patients develop severe and intractable HE after TIPS [76].

Liver transplantation

Episodic or persistent HE in a patient who has cirrhosis constitutes a clinical indication for liver transplant evaluation based on the lower survival associated with the onset of HE [3]. When the precipitating factor is fully treated and the underlying liver function is well preserved (ie, Childs-Pugh class A patients), the option of liver transplantation may be deferred and the patient can be expectantly monitored. Some patients may develop disabling and recurrent HE, however, even with a low MELD score. The low probability of receiving a liver donor for transplantation is problematic for this patient. Although the MELD score prediction of 3-month survival
was not affected by the presence or absence of HE [77], this model was tested using crude, single-center data from a transplant database [77]. Detailed analysis of the effect of the subtypes of HE (severe, disabling, chronic, or recurrent versus precipitated, self-limited, and episodic) on the predictive accuracy of MELD score for survival is necessary because cirrhotic patients who develop severe HE have poor survival, even with a fairly low MELD score [78,79].

Other therapies

Other agents are potentially useful for HE. The ketoanalogues of the branched-chain amino acids (ketoleucine, ketoisocaproate, and ketovaline) could reduce the ammonia pool by amination to the corresponding amino acids, while increasing precursors for protein synthesis and inhibiting protein breakdown [80,81]. Following amination, the ketoanalogues can be effectively incorporated into biologically important proteins [81]. Some clinical studies have indeed shown benefit for HE, but these molecules have not been further developed because of poor palatability [82]. Supplements with branched-chain amino acids have been extensively investigated as potential therapy for HE without proof of efficacy, and branched-chain amino acid is currently rarely used [17,18]. Benzoate may be useful as an ammonia scavenger to treat HE [83,84]. It is approved as an ammonia-reducing agent for urea cycle enzyme deficiency syndromes. It is currently under evaluation as therapy for HE. Opioid and benzodiazepine antagonists, such as naloxone and flumazenil, have been proposed as potential therapies for HE, but have too short-lived effects to be clinically useful [85].

Summary

HE is a common and severe complication of chronic or acute liver failure. Identification and correction of precipitating factors remains the cornerstone of HE therapy. Adjuvant use of nonabsorbable antibiotics and disaccharides, such as rifaximin and lactulose, alone or in combination, help expedite recovery from HE. Liver transplantation is often the most successful long-term therapy for HE.

References


