Current and Emerging Strategies for Treating Hepatic Encephalopathy

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KEYWORDS

• Hepatic encephalopathy • Lactulose • Probiotics
• Acarbose • L-carnitine • Flumazenil

Hepatic encephalopathy (HE) is a constellation of metabolic derangements stemming from hepatic impairment and culminating in neuropsychiatric dysfunction.[1–5] Experts have formulated 2 classification systems that describe the range of etiologies and disease severity engendered by HE. One system is from the World Congress of Gastroenterology, which stratifies the causes of HE into 3 major categories: "*A*" for acute liver failure; "*B*" for portal-systemic shunts, in the absence of intrinsic hepatic insufficiency, that bypass the liver and its detoxifying role; and "*C*" for cirrhosis together with either portal-systemic shunts or portal hypertension.[6] The other system, the West Haven Criteria, is an ordinal scoring system describing the continuum of HE severity, ranging from Grade 1, in which the patient exhibits mild cognitive impairment, to Grade 4, in which the patient becomes comatose. The severity of liver disease may be predictive of HE development,[3] and risk factors include dehydration, constipation, renal failure, sodium and potassium imbalances, infections, gastrointestinal hemorrhage, and hepatocellular carcinoma.[3,4]

Although there is a wide spectrum of HE severity, even milder forms of HE adversely impact patients' quality of life.[7–9] Liver disease and HE may precipitate sleep disorders,[10] impair learning and memory,[11] and deprive patients of their autonomy by affecting motor functions from as simple as walking to as complex as driving.[8,9]

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Almost 15% of patients die while awaiting a liver transplant, and 58% of patients with severe HE die within 1 year.[12]

PATHOGENESIS

Although various chemicals are implicated in HE, it is classically described[1–4] as arising from the liver's inability to convert ammonia (NH_3) to urea. NH_3 accumulates in the brain, disrupting neurochemical function and eventually manifesting as a change in mental status. Situations that allow NH_3-rich blood to avoid the liver's metabolic effect may contribute to HE, including damage to the liver in diseases like cirrhosis[6]; the development of portacaval shunts, which is common in patients with chronic liver disease[13,14]; or the surgical placement of portosystemic shunts in patients with cirrhosis[15] and transplant[16] patients.

Astrocytes, the star-shaped glial cells that help maintain the structural integrity of the central nervous system (CNS) and blood-brain barrier (BBB), are key players in reducing NH_3 levels in the CNS by drawing on the chemical to synthesize glutamate to glutamine.[1,17] On onset of hyperammonianemia, glutamine accumulates in the astrocytes,[18] ultimately leading to an alteration of the structural integrity of the BBB and the potentially overt neuropsychological function.[1,11]

In recent decades, there has been an increasing appreciation for the role that the other neurotoxins play in HE, including hepatic excretion of the trace element manganese, which plays a mediating role with the excitatory neurotransmitter glutamate[4]; and the inability to metabolize phenols[19] and sulfuric by-products[2,5,9,20] from amino acid breakdown in the gastrointestinal (GI) tract. The patient with hepatic insufficiency is also unable to metabolize several chemical by-products of vegetable digestion that mimic the inhibitory effects of the benzodiazepine (BZ) drug class.[4]

CLINICAL MANIFESTATIONS

The classic clinical manifestations of HE comprise a wide variety of neuropsychiatric, neurophysiological, and neurologic symptoms depending on the severity of the disease.[21] The most common changes seen are in the level of consciousness, and in intellectual and neuromuscular function. Changes in consciousness may include subtle changes in personality, sleep-wake cycle and, in later stages of severity, lethargy, stupor, or coma.[21] Changes in intellectual function may include unusual behavior, disorientation to time and place, decreased memory, and confusion.[21] The most common neuromuscular disturbance is a flapping tremor called asterixis.[21] Asterixis is the loss of agonist and antagonist regulation of muscle tone, resulting in an inability to maintain posture. The flapping tremor can be demonstrated by instructing a patient to maintain their arms outstretched with wrists dorsiflexed and fingers spread open. An abrupt loss in flexor tone and a wrist drop in a periodic manner every 2 to 3 seconds is a characteristic sign. One can also look for other signs such as loss of tone in the tongue, pedal dorsiflexion, and fist clenching. Asterixis is usually not present in a comatose patient, so testing for abnormal eye movements, the development of a pyramidal syndrome, and decerebrate posturing[22] would be more helpful in the diagnosis of HE. A pyramidal tract dysfunction includes hypertonia, hyperreflexia, and extension plantar responses, which may later be replaced by hypotonia when coma develops.[21] Additional neuromuscular signs may include the development of a mild parkinsonism characterized by bradykinesia with or without tremor, ataxia, and dsyarthria.[23] The presence of seizures is questionably related to HE, and may be more common in patients who are withdrawing from alcohol or are suffering from a drug-induced or metabolic syndrome.[24]