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Brain Magnetic Resonance in Hepatic Encephalopathy

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The term hepatic encephalopathy (HE) covers a wide spectrum of neuropsychiatric abnormalities caused by portal-systemic shunting. The diagnosis requires demonstration of liver dysfunction or portal-systemic shunts and exclusion of other neurologic disorders. Most patients with this condition have liver dysfunction caused by cirrhosis, but it also occurs in patients with acute liver failure and less commonly, in patients with portal-systemic shunts that are not associated with hepatocellular disease. Various magnetic resonance (MR) techniques have improved our knowledge about the pathophysiology of HE. Proton MR spectroscopy and T1-weighted imaging can detect and quantify accumulations of brain products that are normally metabolized or eliminated such as glutamine and manganese. Other MR techniques such as T2-weighted and diffusion-weighted imaging can identify white matter abnormalities resulting from disturbances in cell volume homeostasis secondary to brain hyperammonemia. Partial or complete recovery of these abnormalities has been observed with normalization of liver function or after successful liver transplantation. MR studies have undoubtedly improved our understanding of the mechanisms involved in the pathogenesis of HE, and some findings can be considered biomarkers for monitoring the effects of therapeutic measures focused on correcting this condition.
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Hepatic encephalopathy (HE) is a term encompassing a wide spectrum of neuropsychiatric abnormalities related to liver dysfunction that can be partially or completely reversible after function normalizes. In most patients with this condition, liver dysfunction is caused by cirrhosis and portal hypertension or portal-systemic shunts. HE is also seen in patients with acute liver failure (ALF), in which it is the hallmark of the disease. Another, less frequent cause of HE is the presence of congenital or acquired shunts that result in portal-systemic bypass without associated hepatocellular disease.[1,2]

The mechanism that causes brain dysfunction in these patients is not fully understood. Over the last years, several studies in humans have applied the technical advances in magnetic resonance (MR) techniques to obtain new insight into the nature of the neuroanatomical substrates and the neurochemical and neurofunctional mechanisms responsible for HE. MR is a safe technique that can obtain morphologic and physiological information about this entity. Furthermore, it does not involve the use of ionizing radiation or radioisotopes; hence, it can be used in longitudinal studies with a relatively large number of subjects. The aim of this article is to describe the clinical features and pathophysiology of HE, review the information that MR techniques have provided about this condition, and examine the role of MR imaging (MRI) in the clinical management of affected patients.

Clinical Features of HE

Patients with HE present central nervous system abnormalities that can affect mental and motor function.[1,3] The mental abnormalities range from mild changes to coma, whereas the motor alterations include rigidity, speech disorders, tremor,

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hyperreflexia, hyporeflexia, Babinski signs, and others,[1,3-6] all of which can affect the quality of life of these patients. Thus, the presence of HE is an important variable to consider in the clinical management strategies and to establish the priority of liver transplantation.[7]

Classification of HE requires a multifactorial approach that takes into consideration the type of hepatic abnormality and the duration and characteristics of the neurologic abnormality.[1] Based on the mechanism causing the hepatic condition, HE can be classified into 3 types: type A, HE associated with ALF; type B, HE associated with portal-systemic bypass (surgical or congenital) without intrinsic hepatocellular disease; and type C, HE associated with cirrhosis and portal hypertension or portal-systemic shunts, the most common type.

According to the length or characteristics of the neurologic changes, HE can be divided into episodic, persistent, or minimal. Episodic HE is characterized by confusional syndrome with impaired mental status, neuromuscular changes, hyperventilation, asterixis, and fetor hepaticus for a short time period and of varying severity. Episodic HE can be subdivided into *spontaneous* when there is no identifiable precipitating factor; *precipitated* when it is caused by precipitating factors such as gastrointestinal hemorrhage, uremia, psychoactive medication, diuretics, dietary indiscretion, infection, constipation, dehydration, hypokalemia or hyperkalemia, or hyponatremia; and *recurrent* when several episodes of episodic HE recur within a short time (usually less than 6 months). Persistent HE is characterized by a clinically evident cognitive deficit that negatively affects daily activities. Minimal HE (MHE), previously known as subclinical HE, refers to the population of patients with cirrhosis or portal-systemic shunts who have subtly abnormal cognitive or neurophysiological function. These abnormalities cannot be detected by standard clinical examination but may produce clinical consequences as they have a detrimental effect on health-related quality of life and on the ability to perform complex tasks such as driving.

Finally, HE can be subdivided into mild (HE grade I) and severe (HE grades II-IV), depending on the severity of autonomy loss.

Pathophysiology of HE

The pathophysiology of HE remains incompletely defined. Several reviews provide detailed information on the available data.[8-13] Briefly, the first hypothesis on the pathogenesis of HE focuses on the effect of abnormal accumulation of certain substances in the blood, such as ammonia or manganese. Ammonia accumulation is widely accepted as being implicated in the development of this condition. Liver failure or the presence of portal-systemic shunts would lead to an increase in blood ammonia concentration, and an amount of ammonia and nitrogenous-related metabolites could cross the blood-brain barrier and enter the central nervous system, thereby affecting its function.

Nonetheless, although ammonia seems to have a central role in the development of HE, there is evidence that other mechanisms also take part. At least 3 elements are reported to contribute to the pathophysiology of HE: (1) a neurotransmission abnormality; (2) injury to the astrocytes, which is likely related to an increase in the intracellular water content; and (3) microglia activation (neuroinflammation). The interrelationships between these mechanisms are uncertain, and their individual importance in the development of HE may differ depending on the type of HE or the stage of the disease.

Neurotransmission abnormalities, likely caused by an imbalance between the inhibitory and excitatory neurotransmission systems toward a net increase of the inhibitory system, are suggested to participate in the pathogenesis of the disease. Several reported findings are consistent with an increase in γ-aminobutyric acid ergic (GABAergic) tone in HE, such as greater resistance to drugs that decrease GABAergic tone, a drop in spontaneous neuron activity caused by GABA agonists, a rise in neuronal GABA synthesis, and visual evoked potentials resembling those induced by drugs that enhance GABAergic tone. There is also evidence indicating disturbed glutamatergic tone, such as an increase in cortical release of glutamate (Glu) and a decrease in Glu uptake by astrocytes and neurons, leading to high Glu levels in the brain extracellular fluid, lower expression of the astroglia-specific Glu transporter, and decreased density of Glu receptors.

An increase in intra-astrocytic glutamine (Gln) due to the high ammonia levels seems to be a key factor for the development of Alzheimer type II astrocytosis. In an osmotic response to this Gln increase, water enters the astrocyte and causes it to swell, which leads to low-grade brain edema. Other factors also seem to be implicated in the development of brain edema, such as ammonia-induced oxidative stress and changes in mitochondrial permeability.

Inflammation secondary to infection, gastrointestinal bleeding, or changes in fecal flora with translocation and increased bacterial overgrowth is also suggested to participate in the pathogenesis of HE. It has been shown that proinflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6) acting synergistically with ammonia can produce brain edema, and an increased production of inflammatory cytokines by neutrophils may enhance this process. Furthermore, microglial activation, which progresses in parallel with the development of HE and brain edema, and concomitant increases in expression of genes coding for proinflammatory cytokines have been documented in patients with HE.

MRI in HE

Although HE is a clinical condition, several neuroimaging techniques, particularly MRI, may eventually be useful for the diagnosis because they can identify and measure the consequences of an increase in substances in the central nervous system, which in normal circumstances are efficiently metabolized by the liver. Classic MR abnormalities in HE include high signal intensity in the globus pallidum on T1-weighted images, likely a reflection of increased tissue concentrations of manganese, and an elevated Gln-Glu peak coupled with decreased myo-inositol (mIns) and choline signals on proton MR spectroscopy (MRS), representing disturbances in cell