AJNR

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AJNR Am J Neuroradiol 2008, 29 (9) 1612-1621
doi: https://doi.org/10.3174/ajnr.A1139
http://www.ajnr.org/content/29/9/1612

REVIEW ARTICLE

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SUMMARY: The term hepatic encephalopathy (HE) includes a spectrum of neuropsychiatric abnormalities occurring in patients with liver dysfunction. Most cases are associated with cirrhosis and portal hypertension or portal-systemic shunts, but the condition can also be seen in patients with acute liver failure and, rarely, with portal-systemic bypass and no associated intrinsic hepatocellular disease. Although HE is a clinical condition, several neuroimaging techniques, particularly MR imaging, may eventually be useful for the diagnosis because they can identify and measure the consequences of central nervous system (CNS) increase in substances that under normal circumstances, are efficiently metabolized by the liver. Classic MR imaging abnormalities include high signal intensity in the globus pallidum on T1-weighted images, likely a reflection of increased tissue concentrations of manganese, and an elevated glutamine/glutamate peak coupled with decreased myo-inositol and choline signals on proton MR spectroscopy, representing disturbances in cell-volume homeostasis secondary to brain hyperammonemia. Recent data have shown that white matter abnormalities, also related to increased CNS ammonia concentration, can also be detected with several MR imaging techniques such as magnetization transfer ratio measurements, fast fluid-attenuated inversion recovery sequences, and diffusion-weighted images. All these MR imaging abnormalities, which return to normal with restoration of liver function, probably reflect the presence of mild diffuse brain edema, which seems to play an essential role in the pathogenesis of HE. It is likely that MR imaging will be increasingly used to evaluate the mechanisms involved in the pathogenesis of HE and to assess the effects of therapeutic measures focused on correcting brain edema in these patients.

Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities occurring in patients with liver dysfunction. Most cases are associated with cirrhosis and portal hypertension or portal-systemic shunts, but the condition can also be seen in patients with acute liver failure and, rarely, with portal-systemic bypass and no associated intrinsic hepatocellular disease.[1,2] The most common clinical pattern in these patients is the development of confusion or coma precipitated by gastrointestinal bleeding, acute superimposed hepatitis, or concomitant infection in a previously asymptomatic patient with cirrhosis. The neurologic manifestations are mainly due to shunt of blood arising from the portal venous bed into the systemic circulation and are reversible once the liver function abnormality or precipitating factor has been corrected. HE can be classified according to the underlying liver disease and the evolution of the neurologic manifestations (Table 1).

Clinical Features

Clinically, HE manifests as a neuropsychiatric syndrome encompassing a wide spectrum of mental and motor disorders.[2,3] The changes in mental status range from subtle cognitive dysfunction to severe coma, whereas the motor function changes include rigidity, disorders of speech production, resting- and movement-induced tremor, delayed diadochokinetic movements, hyper- or hyporeflexia, choreoathetoid movements, Babinski sign, and transient focal symptoms.[3–7] HE can be classified into 3 main groups on the basis of the duration and characteristics of the clinical manifestations[2]: episodic, chronic, and minimal.

Episodic HE

Episodic HE is characterized by the development of a confusional syndrome, including impaired mental state, neuromuscular abnormalities, asterixis, fetor hepaticus, and hyperventilation, which develops during a short period of time and fluctuates in severity. The diagnosis of episodic HE, which requires the exclusion of a pre-existing or evolving dementia, is based on clinical findings and relies on the presence of consistent neurologic manifestations in a patient with severe liver failure and/or portal-systemic shunt surgery. There are no available diagnostic tests to confirm clinically suspected HE. Arterial ammonia analysis adds nothing to the diagnosis of typical patients but is sometimes the clue for diagnosing atypical patients, particularly those with no previous history of liver disease. Neuroimaging techniques also have limited diagnostic value but are required in some atypical patients to exclude other neurologic diseases that can exhibit similar clinical manifestations, such as metabolic encephalopathies, stroke, seizure, meningitis, or encephalitis.

Chronic HE

Chronic HE can be subclassified into relapsing HE and persistent HE. Relapsing HE manifests as frequent episodes of acute HE that may be due to precipitating factors (gastrointestinal hemorrhage, uremia, use of psychoactive medication or diuretics increasing renal ammonia release, dietary indiscretion, infection, constipation, dehydration, hypo- or hyperkalemia, and hyponatremia) but, in most cases, are spontaneous or related to discontinuation of medication. Between acute episodes of HE, which do not differ from those described previously for episodic HE, the patient can be perfectly alert and not show any sign of cognitive dysfunction. However, a careful neurologic examination and neuropsychological tests may re-

Received January 29, 2008; accepted January 30.

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DOI 10.3174/ajnr.A1139

Table 1: Classification of hepatic encephalopathy (HE)

HE	Liver Disease	Extrahepatic Portal-Systemic Shunting	Neurologic Manifestations	Specific Features
Acute episode				
In cirrhosis	Cirrhosis	Variable	Acute confusional state to coma	Usually precipitated
In acute liver failure	Acute liver failure	Absent	Acute confusional state to coma	Frequently complicated by brain edema and intracranial hypertension
Chronic				
Relapsing	Cirrhosis	Severe	Relapsing episodes of encephalopathy	Usually without precipitating factors
Persistent	Cirrhosis	Severe	Persistent cognitive or motor abnormalities	Generally related to surgically induced shunts
Minimal HE	Cirrhosis	Variable	Asymptomatic	Abnormalities revealed by neuropsychological or neurophysiologic tests
In patients with portal-systemic bypass with no intrinsic hepatocellular disease	Absent	Large shunts	Relapsing episodes and persistent abnormalities	Rare disorder, secondary to congenital abnormalities, surgical shunts, or portal vein thrombosis

Table 2: West Haven criteria for semiquantitative grading of HE

Grade	Criteria
1	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition (Sixty-seven percent of patients with cirrhosis may have minimal HE.)
2	Lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, impaired performance of subtraction
3	Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

veal subtle abnormalities, such as extrapyramidal signs and mild cognitive impairment.

Persistent HE refers to manifestations that do not reverse despite adequate treatment. Assessment of the severity of persistent HE is based on the West Haven criteria for semiquantitative grading of mental status, which consider the level of impaired autonomy, changes in consciousness, intellectual function and behavior, and dependence on therapy (Table 2).[2]

The most characteristic manifestations of severe persistent HE are dementia, parkinsonism, or myelopathy in combination with other manifestations of neurologic involvement (ataxia, gait abnormalities, tremor). This clinical picture is seldom seen currently because of the availability of liver transplantation and the small number of patients who undergo portal-systemic shunt surgery.

Minimal HE

Minimal HE, also known as latent or subclinical HE, refers to the population of patients with cirrhosis or portal-systemic shunts who have subtly abnormal cognitive and/or neurophysiologic function. These abnormalities cannot be detected by standard clinical examination[8] but may produce clinical consequences because they have a detrimental impact on health-related quality of life and on the ability to perform complex tasks such as driving.[9]

The absence of clinical evidence of HE is key to the diagnosis of minimal HE and can only be determined by a detailed assessment of the patient's history and a comprehensive neurologic evaluation of consciousness and cognitive and motor functions. The neuropsychological features of minimal HE point to a disorder of executive functioning, particularly selective attention and psychomotor speed, but other abnormalities are also seen.[9,10] A complete psychometric assessment by a neuropsychologist is the best way to know the extent of the patient's cognitive impairment and how it interferes with daily life. However, this evaluation is not easy to carry out because of the cost, complexity, and length of the study. Diagnostic methods that demonstrate central nervous system (CNS) abnormalities attributable to liver failure in a patient with no clinical evidence of HE would be valid as an alternative diagnostic method for minimal HE. Unfortunately, to our knowledge, an arbitrary consensus to define a gold standard to compare the reliability of the different methods has not been reached. The current recommendation is to apply short batteries of diagnostic neuropsychological tests adapted to the cultural characteristics of the population being evaluated. Several neuroimaging techniques such as single-photon emission CT, positron-emission tomography, and MR imaging have shown abnormalities in cerebral blood flow, brain metabolism, and brain structure in patients with minimal HE.[11] However these abnormalities reflect the pathogenic process that underlies the condition, rather than providing diagnostic information.

Pathogenesis of HE

Various hypotheses have been proposed to explain the complex neuropsychiatric syndrome seen in HE. The clinical manifestations of HE appear to reflect primarily a shift in the balance between inhibitory and excitatory neurotransmission toward a net increase of the former, as a consequence of at least 2 factors. The first is downregulation of glutamate receptors following excessive extrasynaptic glutamate accumulation resulting from impaired re-uptake into nerve endings and astrocytes (liver failure inactivates the glutamate transporter in astrocytes). The second factor is an increase in inhibitory neurotransmission due to increased levels of natural benzodiazepines and increased availability of GABA-aminobutyric acid.[12,13]

Pathogenic mechanisms that may be responsible for HE include accumulation in blood of several compounds that are efficiently metabolized by the liver under normal circum-

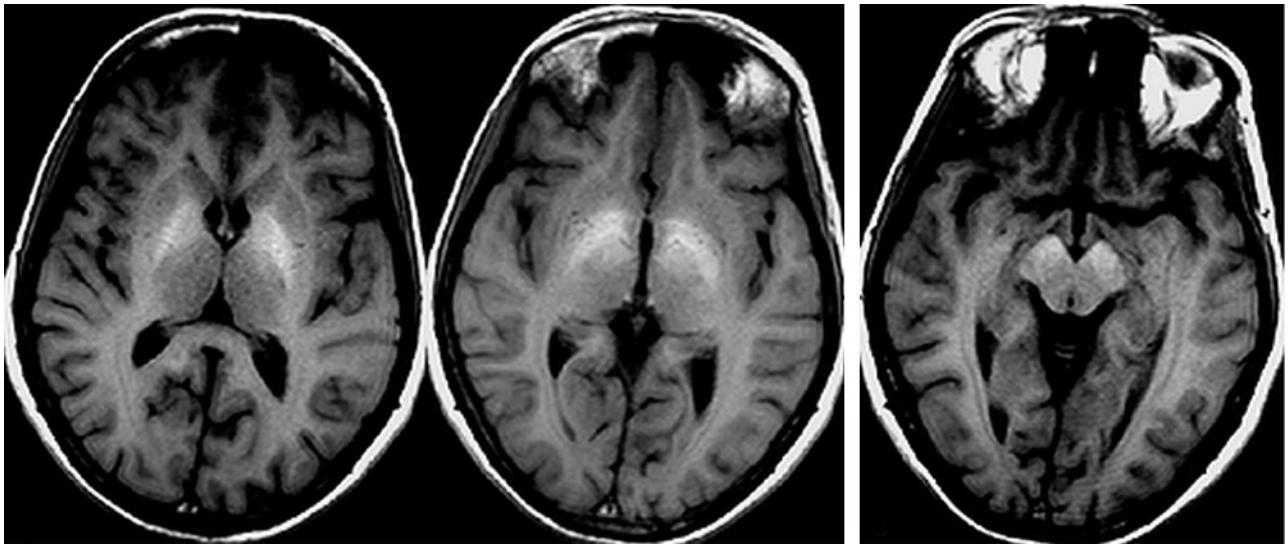

Fig 1. Transverse T1-weighted MR images of the brain in a patient with chronic liver failure and parkinsonism. Observe the bilateral and symmetric high T1 signal-intensity change involving the globus pallidus and the anterior midbrain.

stances, such as manganese and ammonia, which then enter the brain where they induce disturbances in astrocyte and neuron function.[14-17]

Manganese

The CNS is an important target for manganese, an essential element that is normally excreted via the hepatobiliary route.[18] Manganese has a key role in the normal functioning of several enzymes including mitochondrial superoxide dismutase, glutamine synthetase, and phosphoenolpyruvate carboxykinase.[19-21] The metal was first considered to be neurotoxic more than 150 years ago, when workers employed in grinding black oxide of manganese developed an unsteady gait and muscle weakness.[22] Since that time, many cases of manganese neurotoxicity (manganism), a neurologic disease characterized by psychological and neurologic abnormalities, with some similarities to Parkinson disease, have been reported, particularly in miners, smelters, welders, and workers involved in the alloy industry.[23-25] Typically, patients exhibit extrapyramidal changes that include hypokinesia, rigidity, and tremor.

In patients with cirrhosis or portal-systemic shunts, manganese is elevated in plasma and is then transferred to the brain through the blood-brain barrier by several transport systems. This increase in brain manganese has a neurotoxic effect, inducing selective neuronal loss in basal ganglia structures and reactive gliosis. These effects are more prominent in the globus pallidus (particularly the medial segment), the substantia nigra reticulata, and, to a lesser extent, the striatum, with sparing of the substantia nigra pars compacta neurons and striatal dopamine.[14,26-28] This selective vulnerability of basal ganglia structures probably explains the development of parkinsonian manifestations (bradykinesia, rigidity) in HE,[29] which are chronic and usually mild.

Parkinsonian manifestations in HE can be distinguished from idiopathic Parkinson disease by early gait and balance dysfunction, relative absence of resting tremor, presence of mild cognitive impairment at the time of presentation, elevated serum manganese levels, and little or no response to levodopa.[30-34] These differences can be partially explained by the fact that manganese preferentially produces pallidal degeneration, while sparing the nigrostriatal system, in contrast to Parkinson disease, which preferentially damages dopaminergic neurons in the substantia nigra pars compacta.[31]

MR Imaging Marker of Manganese Accumulation within the CNS

Since the introduction of MR imaging in clinical practice, the fact that most patients with cirrhosis or portal-systemic shunts exhibit a bilateral symmetric high signal intensity at the globus pallidus and substantia nigra has been well described (Fig 1).[35,36] The signal intensity may increase after a transjugular intrahepatic portal-systemic stent shunt surgery with transjugular intrahepatic portal-systemic stent placement[37] and reverses after normalization of liver function[36] or after occlusion of congenital portal-systemic shunts.[38] The most plausible explanation for the increased T1 signal intensity is a rise in manganese concentration (a paramagnetic substance) in the CNS, with preferential deposition in the globus pallidus.[39] The arguments favoring the manganese hypothesis include the dramatic blood and CSF manganese increase in patients with cirrhosis and pallidal hyperintensities,[40-42] normalization of MR imaging signal intensity abnormalities and manganese levels after liver transplantation,[36] and the severalfold increase in manganese concentrations from pallidal samples obtained at autopsy in patients with cirrhosis.[43,44]

This manganese-related MR imaging signal-intensity abnormality has also been described in patients without cirrhosis, such as those receiving total parenteral nutrition,[45-48] those with occupational exposure to manganese from welding,[49] and those with noncirrhotic portal vein thrombosis or congenital portal-systemic bypass and no intrinsic hepatocellular disease.[50-52] In all these situations, the MR imaging signal-intensity changes resolve after discontinuation of manganese intake.[45-47] Similar findings were observed in a patient with Alagille syndrome,[53] an autosomal dominant disorder

characterized by cholestasis, intrahepatic bile duct paucity, end stage liver disease, and elevated blood manganese.

Bilateral basal ganglia T1 signal-intensity changes have also been observed in several conditions unrelated to increased brain manganese levels (eg, nonketotic hyperglycemic episodes, hypoxic-ischemic encephalopathy, basal ganglia calcification, neurofibromatosis type I, and Japanese encephalitis), though the high signal intensity occurring in these conditions does not usually show symmetric predominantly pallidal involvement.[54]

Although pallidal hyperintensities are found in approximately 90% of patients with cirrhosis, these signal-intensity alterations are not closely linked to the presence of HE. Patients with cirrhosis and no clinical, neuropsychological, or neurophysiologic signs of HE can also show severe signal-intensity alterations, whereas others with manifest HE may present only slight signal-intensity alterations.[55,56] Moreover, longitudinal studies have shown quick regression of HE after liver transplantation, whereas T1 signal intensity abnormalities need up to 1 year to resolve.[56-59] This clinical MR imaging discrepancy may be explained by the fact that T1 high signal intensity cannot be used as a quantitative measure of tissue manganese because it represents only a semiquantitative measurement of abnormal manganese deposition. Thus, it is possible that manganese accumulation participates in the pathogenesis of HE only after reaching a certain degree, which may not be clearly identified by MR imaging. Recent data support the concept that the presence of parkinsonism is related to the extension of the high signal intensity to midbrain structures (particularly the substantia nigra) because this MR imaging feature is unique to patients with cirrhosis-related parkinsonism (Fig 1).[30]

Ammonia

The main source of ammonia is the gut, and an important amount is of bacterial origin.[60] The concentration of ammonia in portal blood is high and undergoes a high degree of extraction in the liver (90%). Patients with liver failure or portal-systemic shunt surgery have elevated levels of circulating ammonia, which enters the brain through the blood-brain barrier, increasing the brain-blood ammonia concentration ratio (normally in the order of 2) up to fourfold in liver failure. Positron-emission tomography studies by using nitrogen-13 ammonia provide evidence of the increased blood-brain ammonia transfer and brain ammonia utilization rates in patients with chronic liver failure.[61] This hyperammonemia results in profound astrocyte changes, including Alzheimer type II changes in chronic HE and astrocyte swelling in acute HE. In fact, brain edema and increased intracranial pressure are the most important and well-recognized complications of fulminant hepatic failure. The mechanism for astrocyte swelling in acute liver failure remains uncertain but is likely to include excessive generation of osmolytes, mainly glutamine, within the astrocytes[62] as a result of ammonia detoxification through the action of glutamine synthetase. Additionally, abnormalities in intracellular pH and membrane potential can disrupt ion homeostasis and lead to cell swelling.[63]

Nevertheless, although cerebral glutamine increases to a similar extent in both acute and chronic liver failure, brain edema and death from intracranial hypertension are only

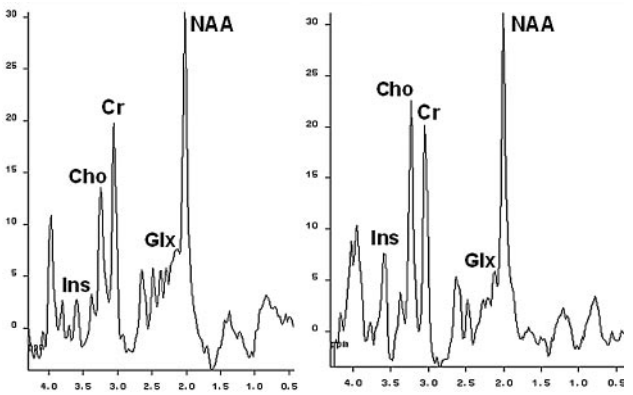

Fig 2. ^{1}H-MR-spectroscopy water-suppressed proton spectra of an 8-mL voxel located in the parietal region including predominantly normal-appearing white matter in a patient with cirrhosis before (left) and after (right) liver transplantation, recorded with a stimulated echo acquisition mode pulse sequence (TR/TE, 1600/20 ms; acquisitions, 256). The main resonances correspond to *N*-acetylaspartate (NAA, 2.0 ppm), glutamine/glutamate (Glx, 2.1–2.5 ppm), creatine/phosphocreatine (Cr, 3.02 ppm), choline-containing compounds (Cho, 3.2 ppm), and myo-inositol (Ins, 3.55 ppm). The initial spectrum shows an increase in the glutamate/glutamine region and a decrease in the myo-inositol and choline resonances. These abnormalities normalized after liver transplantation. Normal NAA indices are seen in both examinations.

rarely complications of chronic liver failure.[64] One possible explanation for this observation is that the relatively more rapid evolution of the syndrome in fulminant hepatic failure may not allow homeostatic compensatory metabolic changes to counteract the osmotic unbalance induced by intra-astrocytic glutamine accumulation. In chronic liver failure, there is enough time for activation of effective compensatory mechanisms of cellular adaptation to the osmotic change[65]: glial accumulation of 1 organic osmolyte, glutamine, should lead to the loss of other organic osmolytes, such as myo-inositol, taurine, and choline.[66] In patients with cirrhosis subjected to ammonia load, this mechanism of osmolar adaptation is clearly reflected in proton MR spectroscopy (^{1}H-MR spectroscopy) studies, which consistently show increases in the glutamine/glutamate signal intensity accompanied by myo-inositol depletion and decreases in the choline signal intensity (Fig 2).[67-73] This osmoregulatory mechanism is activated after liver failure and accounts for the protection against massive edema in chronic liver failure.[74]

The extent of the ^{1}H-MR spectroscopy alterations increases with increasing grade of HE, though these changes have also been observed in patients with cirrhosis and neither clinical nor psychometric or neurophysiologic signs of cerebral dysfunction.[73] Lee et al[68] reported no differences in ^{1}H-MR spectroscopy findings between patients with and without HE and a similar extent of liver dysfunction. Thus, the characteristic ^{1}H-MR spectroscopic changes seem to reflect metabolic more than functional brain alterations.

Some studies assessing the evolution of ^{1}H-MR spectroscopic abnormalities after liver transplantation[57,58,75] have demonstrated their reversibility after liver failure is corrected (Fig 2), though the evolution of these changes differs for each metabolite. The choline peak normalizes earlier than the other peaks and at 1–2 months may even show a small increment over normal values. The glutamine/glutamate peak reaches the normal range at 1–2 months, except in patients with higher pretransplant values, who may take longer.[58,59] The peak myo-

inositol abnormalities normalize slower than the other peaks and may take 3–7 months to reach normal values. This reversibility of ^{1}H-MR spectroscopic abnormalities precedes the disappearance of pallidal hyperintensity after liver transplantation or after occlusion of large portal-systemic shunts[58] and correlates with improvements in the neurologic manifestations of HE.[76]

Diffuse Brain Edema in Chronic Liver Failure

Recent data suggest that despite the adaptive response to increased glutamine concentration, mild astrocyte swelling occurs in the entire spectrum of liver disease and may be partially responsible for the development of HE in chronic liver disease.[74,77,78] A few reports have described brain edema in patients with cirrhosis[64,79] and astrocyte swelling in animal models of minimal HE.[80] In addition, the Alzheimer type II astrocyte, the characteristic neuropathologic finding in patients with cirrhosis, represents a swollen astrocyte, which can be regarded as a manifestation of cerebral edema associated with chronic liver failure.[81] However, conventional MR imaging techniques have not revealed T2-weighted signal-intensity abnormalities within the brain indicating the presence of cerebral edema. Different MR imaging techniques, such as magnetization transfer (MT) imaging,[57,82,83] fast fluid-attenuated inversion recovery (FLAIR) imaging,[84] and diffusion-weighted imaging (DWI),[85,86] which are much more sensitive to changes in brain tissue water content than conventional T2 sequences, have been recently applied for examination of the brain in patients with cirrhosis to obtain data on the attractive hypothesis of the presence of diffuse brain edema, related to hyperammonemia, in patients with chronic liver disease.

MT Imaging

MT imaging is mainly based on the interaction (cross-relaxation) between protons in a relatively free environment (bulk water) and those in which motion is restricted (immobile water).[87] Exchange of this saturated magnetization with free water reduces the signal intensity observed in the subsequent MR image. The degree of signal-intensity loss depends on the attenuation of the macromolecules in a given tissue. Low MT ratios (MTRs) indicate reductions in brain structures able to exchange magnetization with the surrounding water molecules and thereby reflect myelin damage, cell destruction, or changes in water content. Experimental and human studies support the hypothesis that demyelination and axonal loss are the main contributors to the MTR decrease seen in several pathologic conditions, such as experimental autoimmune encephalomyelitis, toxic demyelination, progressive multifocal leukoencephalopathy, human immunodeficiency virus encephalitis, and multiple sclerosis.[88-92] Severe MTR decrease correlates directly with the severity of demyelination and axonal loss, but less severe decrease is more difficult to interpret because inflammation, edema, and moderate demyelination can also contribute to these MTR values.

Different studies have assessed MTR in the brain of patients with cirrhosis.[57,82,83] All these works found low MTR values in all the examined regions of the CNS. Compared with other diseases, the MTR decrease is mild (approximately 10%) and is not accompanied by significant abnormalities on conventional T1- and T2-weighted images. This MTR decrease almost returns to normal values after liver transplantation, thus supporting the hypothesis that these changes reflect mild brain edema.[57] Another explanation for MTR decreases has been proposed by Iwasa et al[93] in a study focusing on basal ganglia abnormalities. On the basis of the correlation between MTR and manganese concentration in phantom experiments, the authors proposed that MTR decreases could be secondary to the accumulation of manganese in the CNS. However, MTR improves rapidly after liver transplantation, whereas pallidal hyperintensity shows a slower disappearance,[49] in keeping with the time course of normalization after manganese intoxication.[47] Furthermore, MTR is low in all brain regions, whereas manganese accumulation predominates in the globus pallidum.[29] The issue of whether the mild brain edema detected by MTR participates in the development of neurologic manifestations is still unresolved. Although a correlation between MTR values and neuropsychological function has not been demonstrated in chronic liver disease, it has been shown that MTR normalization progresses in parallel with the correction of neuropsychological disturbances after liver transplantation.[57]

Fast FLAIR Sequences

Conventional MR imaging is not sensitive enough to detect slight diffuse increases in brain water content. Nonetheless, the following novel MR imaging finding in patients with chronic liver failure has been described: high signal intensity along the hemispheric white matter in or around the corticospinal tract on fast FLAIR T2-weighted images, strikingly similar to signal-intensity abnormalities noted in cases of amyotrophic lateral sclerosis (Fig 3).[84,94] Two possible explanations were given for this previously undescribed signal-intensity abnormality in patients with liver cirrhosis: first, the use of fast FLAIR, a sequence that (at least in the supratentorial compartment) has demonstrated higher sensitivity than conventional T2-weighted sequences for depicting white matter lesions (WMLs).[95] Second, these abnormalities might have been interpreted as a normal finding because fast FLAIR sequences are able to trace the corticospinal tract as a faint symmetric signal-intensity increase in approximately half of healthy adults.[96,97] However, the progressive normalization of this signal-intensity abnormality with improvement of liver function excluded this second interpretation (Fig 3).[84]

The most plausible explanation for the T2 signal-intensity hyperintensity along the hemispheric white matter in or around the corticospinal tract is the presence of mild brain edema, which is further supported from the results of a recent study, which, by using a coregistered MR imaging technique, demonstrated an increase in ventricular volume following medical treatment of HE.[98]

The T2 signal-intensity changes observed in some patients with cirrhosis are quite similar to those observed in amyotrophic lateral sclerosis, in which the pathologic bases are axonal loss, demyelination, or wallerian degeneration.[99] However, none of these pathologic features have been described in association with HE. Moreover, the ^{1}H-MR spectroscopic findings of normal *N*-acetylaspartate indices (a neuronal marker) and low concentrations of choline-containing compounds indicate preservation of axonal attenuation and lack of demyelinating processes (Fig 1).[57] The progressive normalization of

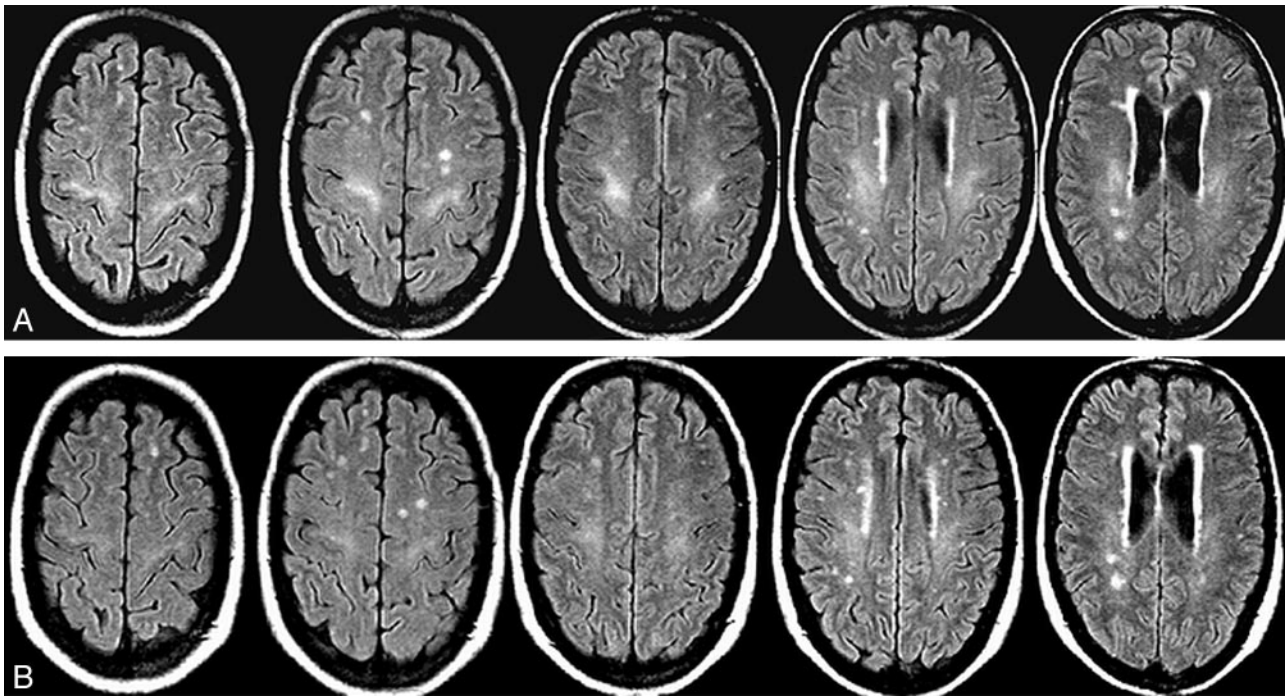

Fig 3. *A,* Transverse T2-weighted fast FLAIR images obtained in a patient with liver cirrhosis during an episode of hepatic encephalopathy. Observe the symmetric areas of increased signal intensity along the corticospinal tract in both cerebral hemispheres. *B,* This signal-intensity abnormality almost completely reverses on a follow-up study obtained few months later, when the patient showed no signs of overt hepatic encephalopathy.

the high-signal-intensity abnormalities in patients with cirrhosis after successful liver transplantation (Fig 2)[84] further supports the hypothesis that edema is the main cause because resolution of demyelination and axonal loss would not be expected after restoration of liver function.

The selective involvement of the white matter within or close to the corticospinal tract observed in patients with cirrhosis may be simply due to a low threshold for visual detection of a widespread white matter alteration because fast FLAIR sequences are able to trace this tract as a faint symmetric signal-intensity increase in approximately half of healthy adults.[96] Alternatively, this selective involvement may reflect a higher vulnerability of this white matter for the development of edema secondary to liver failure. In fact, pyramidal signs are frequently observed in HE[7]; thus, selective involvement of the corticospinal tract in a preclinical state of hepatic encephalopathy could be expected. The reasons for this greater vulnerability of the corticospinal tract are unknown, but they may include higher energy demands and higher susceptibility for excitotoxicity.[100-102]

Involvement of the corticospinal tract on fast FLAIR imaging correlates with abnormalities of transcranial magnetic stimulation (TMS), a noninvasive neurophysiologic method that assesses central motor pathway function.[103] In patients with cirrhosis without overt HE-significant TMS shows increases in central motor conduction time and motor cortical threshold and decreases in motor-evoked potential amplitude.[76] These TMS abnormalities reverse in parallel with the signal intensity of the corticospinal tract on fast FLAIR images after liver transplantation, indicating that this signal-intensity abnormality in patients with chronic liver disease is associated with subclinical functional abnormalities of the corticospinal tract.

White matter focal T2-weighted lesions (WMLs) may be also present in patients with liver cirrhosis with or without overt HE. These lesions resemble those commonly seen in patients with different types of cerebrovascular small-vessel disease (arteriolosclerosis, cerebral amyloid angiopathy, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and in the healthy elderly population (Fig 4).[104] Due to their location and small size, WMLs in patients with cirrhosis can be easily ignored or interpreted as normal involutive or chronic ischemic changes. However in patients with cirrhosis, these lesions decreased their volume with the improvement of HE[105] or after liver transplantation,[106] a fact that is closely correlated with the improvement of neuropsychological function (Fig 4). The partial reversibility of these focal WMLs is on the opposite side of what occurs with focal WMLs attributable to cerebrovascular small-vessel disease. Particularly in patients with hypertension and diabetes, WMLs may increase with time, but never decrease[107-109] and, therefore, are permanently visible on MR imaging, indicating that they represent irreversible tissue damage. The decrease in the volume of WMLs observed in patients with cirrhosis can be explained by changes in the amount of brain edema. It is plausible that liver failure is responsible for low-grade brain edema, which could be exacerbated in areas of small-vessel disease and reverse after liver transplantation.

DWI

MTR and fast FLAIR sequences are highly sensitive in detecting an increase in net water content in the brain tissue. However, they cannot distinguish whether this increase is intracellular or extracellular and, therefore, cannot fully support the theory that mild brain edema in chronic liver failure is second-

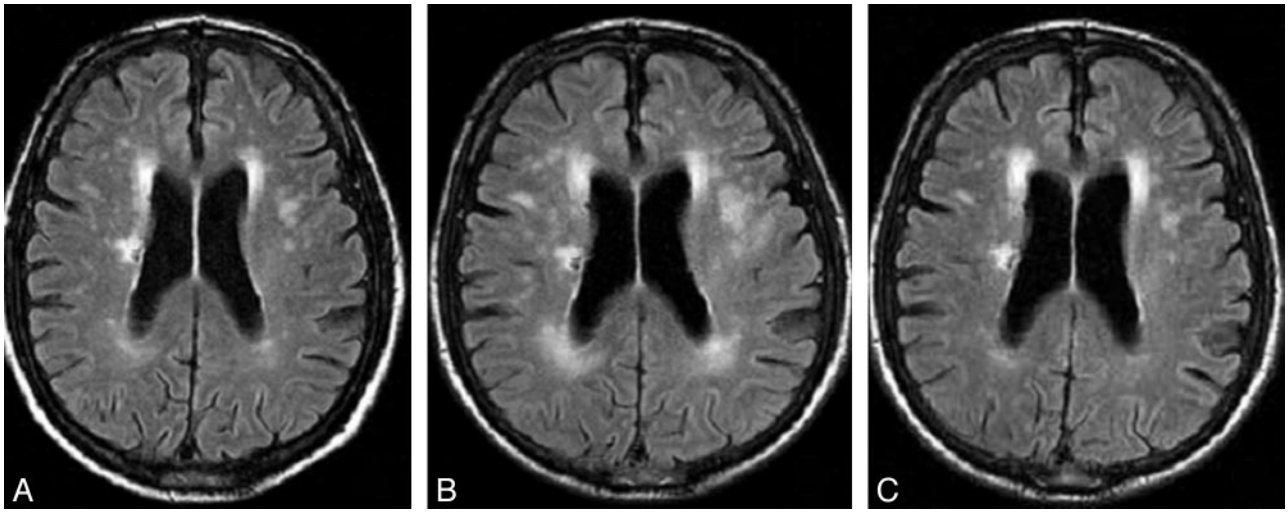

Fig 4. *A*, Baseline MR imaging study (transverse fast FLAIR T2-weighted image) of a 56-year-old patient with hepatitis C cirrhosis without overt hepatic encephalopathy. Multiple focal WMLs in both cerebral hemispheres are attributed to small-vessel disease. *B*, A new scan obtained 2 years later during an episode of hepatic encephalopathy shows marked increase in the size of these focal WMLs. *C*, A new follow-up scan after complete resolution of neurologic symptoms shows a decrease in the size of the WMLs. This last scan was almost identical to the first study. A lacunar infarct is seen in the deep right frontal white matter.

Table 3: MR imaging features in patients with cirrhosis with or without overt HE

	T1WI Sequence	^{1}H-MR spectroscopy	MTR	T2/FLAIR Sequence	DWI
MR imaging abnormalities	Bilateral, symmetric high signal intensity of the globus pallidus and substantia nigra	Increase in glutamine/glutamate signal; depletion of myo-inositol signal; decrease in choline signal; normal NAA signal	Mild (10%) and diffuse decrease in normal-appearing white matter	Diffuse white matter high signal intensities involving predominantly the hemispheric corticospinal tract; focal high-signal T2 lesions in subcortical hemispheric white matter	Increase mean diffusivity in hemispheric white matter; normal fractional anisotropy
Pathogenesis	Increased brain tissue concentration of manganese	Osmolar adaptation of intra-astrocytic accumulation of glutamine	Mild and diffuse brain edema	Mild and diffuse brain edema	Interstitial brain edema
Functional consequences	Parkinsonism (particularly if substantia nigra is involved)	Overt hepatic encephalopathy (particularly with increase in glutamine/glutamate)	Functional abnormalities of the corticospinal tract on TMS	Functional abnormalities of the corticospinal tract on TMS; cognitive impairment	Cognitive impairment

Note:—T1WI Indicates T1-weighted imaging; NAA, *N*-acetylaspartate; TMS, transcranial magnetic stimulation; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; MTR, magnetization transfer ratio.

ary to astrocyte swelling. This issue could be resolved by DWI, which could potentially locate the compartment where the water increase is more prominent.

Recent data on the use of mean diffusivity measurements within normal-appearing white matter of patients with cirrhosis have yielded unexpected results. Different studies have shown significant increase in brain water diffusivity, which was more pronounced with increasing grade of HE.[85,86,110] These diffusivity values correlated with neuropsychological impairment and with serum venous ammonia. These findings, according to the basic understanding of diffusivity,[111] probably reflect an accumulation of water in the extracellular compartment and, therefore, do not support the hypothesis of astrocytic swelling as the cause of diffuse brain edema in chronic liver failure.

The exact mechanism of this increase in extracellular fluid is not known. Plausible explanations would be the extracellular migration of the macromolecules during the cellular osmoregulatory mechanism induced by the increase in astrocytic glutamate or an increased blood-brain barrier permeability. In fact, hyperammonemia may induce an increase in blood-brain barrier permeability,[112] which will tend to favor cerebral capillary water influx to the brain. Moreover, Alzheimer type II astrocytes, a common abnormality in HE that was interpreted as a sign of astrocyte swelling, may correspond indeed to cellular damage and lose of cellular shape caused by oxidative stress, instead of intracellular edema.[113] Another proposed explanation is that exposure of the brain to ammonia results in reduced expression of genes coding for key astrocytic proteins, such as the structural glial fibrillary acidic protein (GFAP), a cytoplasmatic filamentous protein that constitutes a major integral part of the cellular component in mature astrocytes.[114,115] Reduced expression of GFAP induces morphologic changes in astrocytes, favoring diffusivity in the

extracellular space.[116] In acute liver failure, mean diffusivity values have been shown to be reduced,[117] therefore supporting an increased cell volume secondary to massive intra-astrocytic increase of glutamine as the mechanism of brain edema. Therefore, 2 different type of brain edema may exist in liver failure, intracellular in acute forms and probably interstitial in chronic forms.

Conclusions

Different MR imaging data obtained in patients with different types of liver failure have improved our understanding of the pathogenesis of HE, such as the involvement of manganese deposition in parkinsonism and the development of mild grade cerebral edema and osmotic abnormalities secondary to the increase in brain ammonia (Table 3). All these data support the use of MR imaging as a useful tool to study the pathogenesis of HE in humans, for the adequate interpretation of cognitive impairment in patients with cirrhosis, and for assessing the effects of therapeutic measures focused in correcting this disorder.

Acknowledgment

We thank Celine Cavallo for English language assistance.

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