Magnetic Resonance Imaging and Spectroscopy in Hepatic Encephalopathy

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Hepatic encephalopathy is a brain alteration associated to liver failure that produces cognitive impairments at long term. Neuroimaging are non-invasive methods for the study of the brain by means of spectroscopy and imaging techniques. These technologies give huge information about cerebral metabolism and water distribution to explore brain pathways involved in the pathogenesis of hepatic encephalopathy. Furthermore, new magnetic resonance implementations such as voxel-based morphometry or resting-state functional magnetic resonance imaging allow studying brain atrophy and neuronal connectivity of the cerebral network involved in the neurocognitive impairments observed in the patients. The development of magnetic resonance technology will generate handy tools for the brain study of liver failure to elucidate the time-course of the pathology and thus to obtain an early diagnosis of cerebral complications. (J Clin Exp Hepatol 2015;5:S69–S74)

Hepatic encephalopathy (HE), a liver failure complication, is a metabolic encephalopathy that covers a wide range of neurological manifestations, from subtle cognitive deficits (MHE: minimal HE) to deep coma (overt HE). The ammonia accumulation and/or inflammation seem to be involved in the pathogenesis of HE; however, the time-course of these events is not well established. Classically, HE is classified in three types according to the origin of liver injury, type A HE is related to acute liver failure; type B HE to porto-systemic shunts; and type C to cirrhosis that additionally could be minimal (MHE) or overt (in that case could be episodic or persistent).[1]

Patients with MHE have not an apparent cognitive impairment and it is only detectable by some psychometric tests such as critical flicker frequency (CFF) or psychometric hepatic encephalopathy score (PHES). However, it is difficult to distinguish those cirrhotic patients with MHE from those without HE because of the lack of a "gold" standard in the diagnostic criteria of MHE. In addition, it was estimated that in the future some of these patients with MHE develops an overt HE. For this reason, an early diagnostic of MHE is crucial to avoid future cognitive complications.

Patients with overt HE have brain alterations, from mild upsets (e.g. confusion, depression, somnolence) to deep coma. The grades of HE are well established by neurological assessment (West Haven). Recently, operational definition of the severity of HE according to West Haven have been proposed (HESA: HE Scoring Algorithm).[2] The HE grade, the number of episodes and the persistence of HE is important to minimize the long-term cognitive detriment of the patients, especially with chronic liver disease and these factors should be considered in the clinical management (e.g. treatment or transplant).[3]

MAGNETIC RESONANCE

The magnetic resonance (MR) is a non-invasive technique used for the assessment of HE degree by spectroscopic and imaging clinical studies. Almost all studies in patients are based on proton signals from metabolites or water content among tissues and organs, respectively. These evaluations allow studying metabolic composition, anatomical structures or functional brain connectivity, according to the processing and the complexity of the sample.

MR spectroscopy (MRS) provides information about the metabolic status of the tissues. MRS consists in evaluating the proton relaxation of a small volume of tissue to obtain a spectrum of signals depending on frequency in which each metabolite has a specific position along the spectrum. This allows the identification of a compound in a mixture of metabolites and the metabolite concentration through the area below the peak. Proton MRS in brain

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Abbreviations: ADC: apparent diffusion coefficient; CFF: critical flicker frequency; fMRI: functional magnetic resonance imaging; HE: hepatic encephalopathy; MR: magnetic resonance; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; MT: magnetization transfer; MTR: magnetization transfer ratio; NAA: N-acetyl aspartate; PHES: psychometric hepatic encephalopathy score; VBM: voxel-based morphometry
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mainly detects lactate (an end-product of anaerobic glycolysis); N-acetyl aspartate (NAA) (considered as neuronal marker); glutamate and glutamine (substrate and precursor of the amino acid involved in the excitatory neurotransmission); creatine and phosphocreatine (metabolites of energetic reservoir); choline derivates (cell membrane components); and myo-inositol (putative glia marker with unknown function).[4]

MR imaging (MRI) is based on proton signals from water content among tissues and organs. The conventional images in MRI are proton density in which the contrast is proportional to the amount of hydrogen, T1-weighted images that provide information of the T1 relaxation time of the tissues (fat tissue is bright while water is dark) and T2-weighted images give transverse relaxation of tissue trough T2 relaxation time (fluids are more brilliant than fat tissue).[5]

Techniques that are more sophisticated allow quantifying brain alterations of different pathologies such as water content, atrophy or connectivity. Magnetic transfer ratio (MTR) images offers contrast from the interactions between the protons in free fluid and those protons bound in macromolecules and both type of protons are in constant exchange. Low MTRs indicate reductions in brain structures in which exchange magnetization with the surrounding water molecules and could reflect myelin damage, cell destruction, or changes in water content.[5] Diffusion imaging shows local water diffusion by the apparent diffusion coefficient (ADC) and a variant of this imaging, diffusion tensor imaging, gets different anisotropic parameters to study the structural integrity, additionally.[6] Furthermore, the amount of brain water has also absolutely quantified using a complex method of MR.[7]

The volumetric measurements provide tools to determine brain atrophy by different strategies. Classically, these studies consisted in drawing regions of interest of whole brain or subparts (e.g. ventricles) on the brain images and calculating the volume enclosed.[3] In recent years, voxel-based morphometry (VBM) has developed to analyze differences in brain anatomy using diverse statistical approaches.[8]

Currently, a huge MR area has been developed to explore brain activity by functional MRI (fMRI).[9] These techniques are based in the assessment of local blood flow and hemoglobin oxygenation changes due to the metabolic changes because of brain activity. A subdivision is the resting-state fMRI that consists in studying the brain when the subject is not performing an explicit task due to cerebral activity.[10] These studies are useful to explore the brain's functional connectivity as well as to examine alterations in neurological or psychiatric diseases.

MAGNETIC RESONANCE STUDIES IN HEPATIC ENCEPHALOPATHY

Magnetic resonance (MR) is a non-invasive technique used for the assessment of HE degree by spectroscopic and imaging clinical studies. However, almost all clinical MR studies have performed in patients whose at the moment

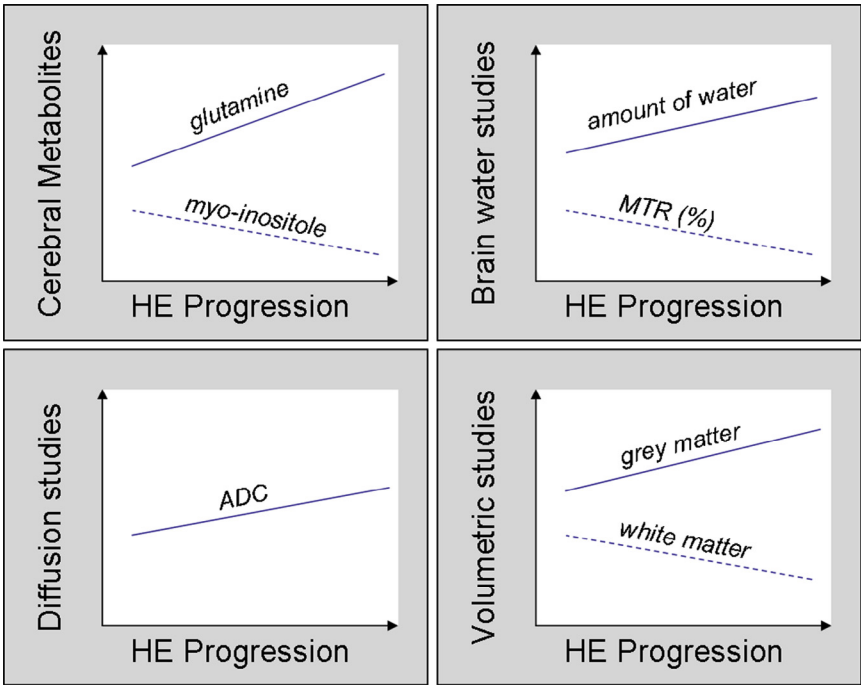

Figure 1 Schema of the general results found in MR studies according to the progression of HE.

Table 1 Proton magnetic resonance (MR) spectroscopy of cirrhotic patients with different grades of hepatic encephalopathy (HE).

MR study	Subjects	*n*	Changes of ratios versus creatine compared to controls group			
			Glutamine	Myo-Inositol	Choline	NAA
(Poveda et al, 2010)	Control	9				
	No HE	9	↑	↓	≈	≈
	Overt HE	24	↑[a,b]	↓	≈	≈
(Laubenberger et al, 1997)	Control	20				
	No HE	24	↑	↓	≈	≈
	MHE	4	↑	↓	≈	≈
	Overt HE (I/II/III/IV)	11 (4/6/0/1)	↑[b,c]	↓[b]	≈	↓[b]
(Tarasow et al, 2003)	Control	20				
	No HE	20	↑	↓	↓	≈
	Overt HE (I/II/III/IV)	14 (11/3/0/0)	↑	↓[b]	↓	≈
(Cordoba et al, 2001)	Control	10				
	No HE	24	↑	↓		
	MHE		↑[b]	↓[b]		
(Chavarria et al, 2013)	Control	8			≈	≈
	No HE	7	↑	↓	≈	≈
	Overt HE (I/II/III/IV)	10 (5/3/0/2)	↑[a,c]	↓	↓[c]	≈

[a]Decrease of values after recovery.
[b]Significant changes between cirrhotic patients without HE (no HE), with minimal HE (MHE) or with overt HE.
[c]Significant changes between the different HE grades (I/II/III/IV) in overt HE determined by West-Haven criteria where patients with grade I, exhibited lack of awareness; grade II, lethargy or apathy; grade III, somnolence to semi stupor; and grade IV, were in coma.

of the study did not have clear evidences of HE (cirrhotic patients without HE or with MHE) although those of them have suffered a previous episode of HE. On the contrary, only few articles were analyzed MR parameters during an episode of HE due to the complexity of management of these patients. These evaluations allow studying metabolic composition, brain edema, anatomical structures or functional brain connectivity alterations during one episode of HE (Figure 1).

Cerebral Metabolism

MRS followed the alterations of brain metabolites in the patients with cirrhosis. Proton spectroscopy studies showed a progressive increase in glutamine and glutamate peak according to the severity of HE (Table 1). In addition, a decrease in glutamine and glutamate peak was found after clinical resolution of HE episode.[11,12] Myo-inositol had gradually decreased with the HE degree even though it did not find changes in overt HE probably due to technical limitations. Both metabolites changes are associated to compensatory mechanisms in the brain due to a cerebral osmolytes regulation produced by the increase in ammonia. On the contrary, the studies did not demonstrate any changes neither in choline derivates nor NAA except in advances stages of HE.[12–14] These results are compatible with a loss of neurons that could be responsible to neurocognitive impairments observed in the patients.[3]

Brian Water Assessment

Cirrhotic patients with HE showed an increase in cerebral water that was analyzed directly or indirectly by MR (Table 2). MTR studies exhibited a continuous decrease of MTR according to the degree of HE. This indirect parameter denoted an increase in brain water. In addition, the loss of MTR increased in spatial extent and severity in patients with overt HE.[15] The augment of water was related with the increase of cerebral ammonia but the time-course of the events was completely not clear. Quantitative MR experiments proved this rise of brain water in cirrhotic patients according to the HE progression.[7]

The distribution of cerebral water in cirrhotic patients can be studied by means of diffusion studies. The interpretation of the results is still a matter of debate but the majority of authors interpret that an increase in diffusion corresponds to a rise of extracellular brain water. There are only two studies in humans that have applied diffusion weighted imaging during an overt episode of HE (Table 3). While *Poveda* and colleagues showed no changes in ADC during HE[11]; in our study we found an increase in ADC values in cirrhotic patients specially in those with high-grade HE[12]. Indeed, both studies also showed a decrease

Table 2 Brain water MR assessments of cirrhotic patients with different grades of hepatic encephalopathy (HE).

MR study	Subjects	*n*	MR parameters compared to control group	
			MTR (%)	Amount of water
(Poveda et al, 2010)	Control	9		
	No HE	9	↓[a]	
	Overt HE	54	↓[a]	
(Miese et al, 2009)	Control	18		
	No HE	5	↓[a]	
	MHE	3	↓[a]	
	Overt HE (I/II/III/IV)	11 (6/5/0/0)	↓[a,b]	
(Cordoba et al, 2001)	Control	10		
	No HE	24	↓[a]	
	MHE		↓[a]	
(Shah et al, 2008)	Control	7		
	No HE	13		↑[a]
	MHE	12		↑[a]
	Overt HE	13		↑[a]

[a]Significant changes between cirrhotic patients without HE (no HE), with minimal HE (MHE) or with overt HE.
[b]Significant changes between the different HE grades (I/II/III/IV) in overt HE determined by West-Haven criteria where patients with grade I, exhibited lack of awareness; grade II, lethargy or apathy; grade III, somnolence to semi stupor; and grade IV, were in coma.

in ADC after the resolution of HE, supporting an increase of extracellular water during episodic HE in chronic liver failure. The behavior of diffusion parameters was different from those observed in different liver failure (acute or acute-on-chronic liver failure) (Table 4). Acute liver failure patients exhibited a decrease in ADC attributed to an increase of intracellular water.[16–18] Controversially, acute-on-chronic patients showed the same alterations in diffusion tensor parameters of liver failure without changes in ADC that could suggest to the presence of mixed cerebral edema (intracellular and extracellular).[19] These results show the complexity of brain edema in physiopathology of liver failure.

Atrophy

VBM are a new MR strategy to perform volumetric studies of brain and subsequently to address atrophy (Table 5). MR experiments with this approach showed that cirrhotic patients had many areas with a decrease in gray matter volume and an increase in white matter volume, compared to

Table 3 Diffusion studies of cirrhotic patients with different grades of hepatic encephalopathy (HE).

MR study	Subjects	*n*	ADC values	
			HE episode	HE recovery
(Poveda et al, 2010)	Control	9		
	No HE	9	≈	
	Overt HE	24	≈	↓
(Chavarria et al, 2013)	Control	8		
	No HE	7	↑[a]	
	Overt HE (I/II/III/IV)	10 (5/3/0/2)	↑[b]	↓

[a]Significant changes between cirrhotic patients without HE (no HE), with minimal HE (MHE) or with overt HE.
[b]Significant changes between the different HE grades (I/II/III/IV) in overt HE determined by West-Haven criteria where patients with grade I, exhibited lack of awareness; grade II, lethargy or apathy; grade III, somnolence to semi stupor; and grade IV, were in coma.

healthy controls, which were further aggravated with the HE progression.[20,21] These results are compatible with brain atrophy because of the severity of HE. However, *Tarasow* and co-workers obtained no differences in the atrophy between cirrhotic patients and overt HE.[14]

Cognitive Function Evaluation

Recently, a cognitive detriment in cirrhotic patients was made obvious especially in those patients that suffered previous episodes of HE. For this reason, resting-state fMRI was developed to evaluate functional connectivity within the default-mode network. Neurocognitive impairments were observed in cirrhotic patients after an apparent recovery of the overt HE (with MHE or without HE and a previous episode of HE), despite normal mental status.[22,23] In addition, *Zhang* and colleagues discovered a reduced

Table 4 Diffusion studies according to the origin of liver failure.

MR studies	Liver failure	MR parameters compared to control group			
		ADC/MD	Diffusion tensor parameters		
			FA	CL	CS
(Nath et al 2008)	Chronic	↑	↓	↓	↑
(Nath et al 2008)	Acute-on-chronic	≈	↓	↓	↑
(Ranjan et al 2005; Rai et al 2008; Saksena et al 2008)	Acute	↓	↓	↓	↑

MR parameters: ADC, apparent diffusion coefficient; MD, mean diffusivity; FA, fractional anisotropy; CL, lineal anisotropy; CS, spherical anisotropy.

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Table 5 Volumetric studies by magnetic resonance (MR) of cirrhotic patients with different grades of hepatic encephalopathy (HE).

MR study	Subjects	*n*	Brain density or brain volume compared to control	
			Gray matter	White matter
(Guevara et al, 2011)[a]	Control	51		
	No HE	48	↓	↓
(Zhang et al, 2012)[b]	Control	40		
	No HE	31	↓[c]	↑[c]
	MHE	18	↓[c]	↑[c]
	Overt HE	11	↓[c]	↑[c]

[a]Voxel-based morphometry study of brain density.
[b]Voxel-based morphometry study of brain volume.
[c]Significant changes between cirrhotic patients without HE (no HE), with minimal HE (MHE) or with overt HE.

tendency of the functional connectivity within the default-mode network in patients with an overt episode of HE.[24]

CONCLUSION

HE seems to be an important factor for the follow-up of cirrhotic patients in particular for the cognitive function. In addition, severe brain atrophy is likely involved in the mechanisms underlying incomplete resolution of overt HE. Both functional and structural cerebral impairments after resolution of an overt episode of HE reveals irreversible effects induced by HE on brain function and provide a basis for further evolution of the disease. A refinement of HE diagnostic above MHE could be decisive to avoid future cognitive dysfunction. Maybe other parameters could be taking into account for a better diagnosis of MHE and thus to prevent early decline of cognitive function.

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CONFLICTS OF INTEREST

All authors have none to declare.

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