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STATE OF THE ART

Current Stance of Magnetic Resonance Imaging in the Diagnosis and Monitoring of Hepatic Encephalopathy

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ABSTRACT

Objectives: *Hepatic encephalopathy is a complex of neuropsychiatric manifestations in patients with acute or chronic liver insufficiency and/or porto-systemic shunts.*

Material and methods: *The diagnostic can be sustained by various elements, clinical and paraclinical. Selected patients with hepatic encephalopathy have been investigated by Magnetic Resonance, in parallel with specific biochemical analysis.*

Outcomes: *This paper emphasizes the importance of Magnetic Resonance Imaging in an accurate diagnosis and patient monitoring after treatment.*

Conclusions: *Magnetic Resonance Spectroscopy has a substantial role, showing even minute metabolite ratio changes, with a potential in investigating minimal hepatic encephalopathy.*

Keywords: hepatic encephalopathy, magnetic resonance imaging, magnetic resonance spectroscopy, minimal hepatic encephalopathy

INTRODUCTION

Hepatic encephalopathy (HE) is a syndrome defined by a wide range of neuropsychiatric symptoms in patients with chronic or acute liver disease. The diagnosis is both clinical and paraclinical (biological and imaging), and may sometimes be difficult in patients with concurring central nervous system diseases. It can be even more complicated in patients with only subtle neurologic and psychological changes, at times difficult to assess by the patient's entourage or even by the patient himself. This is called minimal hepatic encephalopathy and represents a subject of debate and increasing interest.

The grading of HE is performed using the West-Haven criteria (1). In cases of frank HE, memory and attention deficit, asterixis and foe-

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tor haepaticus lead to the diagnosis. For minimal HE, a range of neuropsychological tests are available.

Laboratory findings usually report a high ammonia level in patients with HE, with a specificity of about 90% (2) but with the mention that the blood must be arterial or free venous (blood drawn from the arm with a tourniquet is expected to have falsely increased ammonia) (3).

Electroencephalogram and visual evoked responses have low significance in common practice. Computed Tomography and Magnetic Resonance Imaging (MRI) have an important role in excluding pathology with similar symptoms. Additionally, MRI has specific advantages in the positive diagnosis, which will be explored in the following. ❑

ROLE OF MRI IN THE DIAGNOSIS OF HEPATIC ENCEPHALOPATHY

1. General investigation protocol to be employed

A dedicated protocol for the diagnosis and monitoring of hepatic encephalopathy should include routine axial T1 and T2 spin-echo sequences, dark-fluid T2 images, diffusion weighted imaging, T2* gradient echo sequences, and, if available, magnetic resonance spectroscopy should be applied, both single and multivoxel.

High-field magnetic resonance can provide shorter investigation times and a certain improvement in image resolution (4), but since availability is limited in most centers, the most common MR machines, as well as the one used to obtain the images in this study, use a 1.5T field strength.

2. Demonstrating typical manganese deposits in the basal ganglia

Manganese is an element with an important role in the normal functioning of several enzymes such as superoxide dismutase, some synthetases and peroxidases, and can be neurotoxic in high amounts. Manganese is excreted biliary, and in cases of liver failure or porto-systemic shunts, it can accumulate in the plasma, pass the blood-brain barrier (BBB) and deposit with predilection in the globus pallidus (bilaterally). These deposits correlate with neuromotor symptoms such as Parkinsonian manifestations (5).

MRI identifies the manganese deposits as typical bilateral high signal intensities in the globus pallidus on the T1 Spin Echo weighted images (Figure 1). Nevertheless, these changes do not always correlate with the presence and degree of HE, and also, there are cases of severe HE with just discrete signal abnormalities, thus being fair to consider they more likely represent stigmata of a chronic liver disease (6).

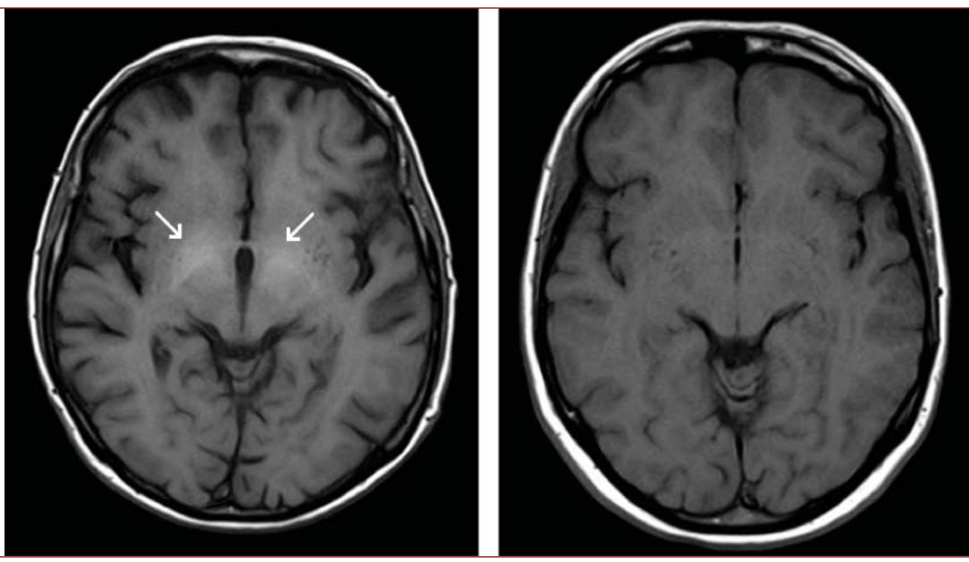

FIGURE 1. T1 Spin Echo weighted images, located at the level of the basal ganglia. Note the hyperintensity of globus pallidus bilaterally (arrow) in the patient with HE (left) compared to a normal patient (right). This sequence is commonly performed in an oblique axial plane (bicommissural).

3. Demonstrating diffuse cerebral edema associated with astrocyte swelling

Accumulation of osmotically active intracellular compounds such as glutamine can produce swelling of the astrocyte cells, with clinical impact. MRI can demonstrate cerebral edema by specific sequences. T2 weighted images, although generally useful in quantifying tissue water distribution, has little sensitivity in the detection of cerebral edema in the context of HE (Figure 2a). Generally, cortical edema spares perirolandic and occipital regions. Other imaging techniques such as diffusion weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) have a greater importance in this direction.

DWI can prove water restriction in different compartments, providing an insight into the pathogenesis of the edema (Figure 2b). Characteristic changes are an extracellular water accumulation which is most likely due to a combination of the migration of intracellular water from astrocyte swelling and an increased blood-brain barrier permeability which facilitates water rush to the brain (7).

FLAIR sequences may show a signal anomaly in the white subcortical matter and corticospinal tracts, bilaterally (Figure 2c). This has been interpreted as being caused by a moderate cerebral edema, although similar findings are demonstrated in almost half of the normal subjects. The correlation between the specific location and anomaly type and the pyramidal signs observed in HE seems plausible, especially considering that resolution of clinical symptoms are doubled by a normalization of the signal in the corticospinal tracts after treatment (8).

4. Directly quantifying brain metabolites through Magnetic Resonance Spectroscopy

Magnetic Resonance Spectroscopy (MRS) is a non-invasive imaging technique which can identify a series of molecules inside a defined volume of interest (VOI). Characteristically, in HE, MRS demonstrates a decrease of Myoinositol (mI)/Creatine (Cr) and Choline/Creatine ratios, the increase of glutamine/glutamate (Glx) peak and Glx/Cr ratio, as well as a decrease of Choline (Cho) peak (9). Currently, the main pathogenic hypothesis accepted is that excess ammonia due to impaired liver function and/or porto-systemic shunts crosses the BBB and starts to accumulate. It can only be cleared during the glutamine synthesis, leading to an increase of this particular osmolyte. This increase induces astrocyte swelling. One mechanism of protection is myo-inositol depletion (10). Both glutamine and myo-inositol can be identified and measured my MRS, giving objective data which can be easily interpreted in dynamic, after treatment (Figure 3). These changes are very specific, and in a high correlation with the onset and degree of HE (11). Moreover, changes in MRS precede the other MRI signs, offering the possibility of an early diagnosis. High-field MRS, with homogenous magnetic field, can demonstrate even subtle alterations in the normal MR spectrum of the fore-mentioned metabolites, proving a great use in minimal HE (MHE) diagnosis (12). MRS in patients with suspected MHE should be examined with short TE MRS. Most papers have used standardized single voxel locations in the mesial occipital gray matter, and parietal white matter (13,14). One downside is that MRS may

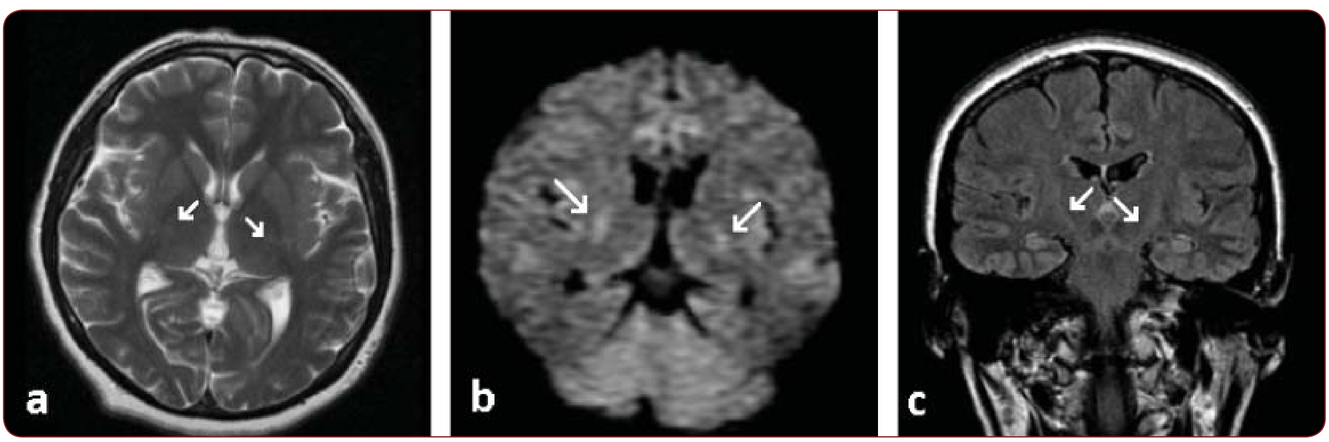

FIGURE 2. Hyperintensities in the corticospinal tracts bilaterally (arrows), more prominent on the left side, in the same patient. T2 TSE axial plane (a), DWI (b) and FLAIR coronal plane (c) sequences.

demonstrate a relatively low sensitivity in the detection of MHE, ranging from 60% to 90%, which seems to be caused by magnetic field inhomogeneities related to the performance of the MR machine or to its maintenance condition (15,16). Since there is no gold-standard for diagnosing minimal hepatic encephalopathy, it being rather a clinical than imaging diagnosis, the role MRS seems to play is important in regard to its high specificity, as this particular spectrum profile has virtually no differential diagnosis, being found exclusively in this condition. The limits imposed by the low sensitivity need to be treated with caution by the clinician, in direct proportion with the clinical suspicion and other diagnostic information such as psychosomatic testing. Also, the high cost and overall low availability of this method could represent an impediment, making MRS just an alternative step in the diagnostic protocol, and not an essential element, for the time being.

5. Other directions and techniques

MTI (Magnetization Transfer Imaging) is an MRI application used to evaluate components other than water in a tissue, by taking advantage of the property of magnetization transfer between free water and macromolecules (17). Some studies found statistically significant changes in the frontal and posterior white matter, thalamus and basal ganglia, consistent with HE, yet no one specific area of the brain presented exclusive MTI features in overt HE (18).

Diffusion Tensor MR imaging demonstrates the presence of low mean diffusivity in various grey and white matter regions in patients with cytotoxic cerebral edema in acute liver failure (19). High mean diffusivity is found in patients with chronic liver disease which correlates with results of specific neuropsychiatric tests, and also shows reversibility along with improvements of said tests. These can pin-point to the specific moment of transition from minimal to overt HE in patients with chronic liver disease (20).

T2* Gradient Echo imaging is one of the oldest sequences used in magnetic resonance, but along with the technological progress it has been refined and is currently applicable in the diagnosis of hepatic encephalopathy at 3T by demonstrating putative iron loads in the frontal-basal ganglia-thalamocortical circuits which seems to correlate with the degree of cognitive impairment, especially in minimal HE (21). ❑

CONCLUSION

Hepatic encephalopathy has both morphological and functional cerebral correspondences. Magnetic Resonance Imaging can identify structural anomalies such as elementary deposits and cerebral edema, as can also provide functional data regarding various mo-

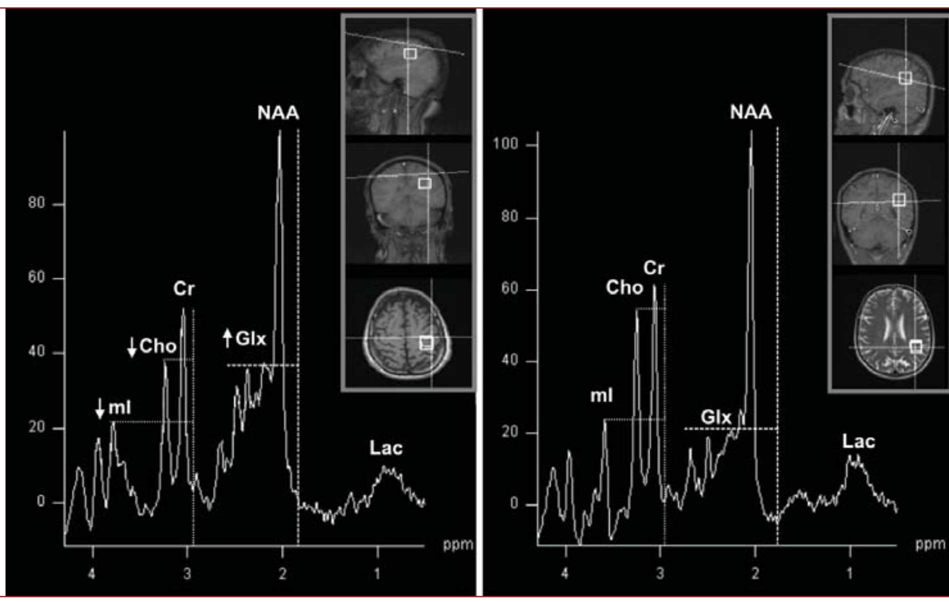

FIGURE 3. Single voxel MR spectroscopy investigation in a patient with HE (left) compared to a normal patient (right). Typical and highly specific changes, represented by an increased Glutamate-Glutamine-Gamaaminobutyric acid (Glx) peak accompanied by a decrease of the myoinositol (mI) and Creatine (Cr) peaks. Voxel location in each case is referenced in corresponding thumbnails.

lecule imbalances in the brain. MRS also has an important role in minimal HE detection and characterization, and should be considered as a step in the diagnostic protocol. New modalities and techniques emerge, which can give insight to the pathophysiology of hepatic encephalopathy and improve the diagnostic accuracy and ease of management of these patients.

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