JOURNAL
OF HEPATOLOGY

Magnetic resonance spectroscopy: A surrogate marker of hepatic encephalopathy?

To the Editor:

The pathophysiology of hepatic encephalopathy (HE) is still controversial but the major role of systemic inflammation in conjunction with hyperammonemia is proven.[1] An intermediate step seems related to the degradation of ammonia into glutamine. Once the liver function is compromised, only muscle cells and astrocytes are able to produce glutamine through their glutamine synthetase expression. It is noticeable that the decrease in muscle mass could constitute a triggering event in HE occurrence and that glutamine induces the astrocytic cytotoxic edema responsible for altered astrocyte functioning. Other factors could further contribute to this pathophysiology: bile acids, mercaptans, benzodiazepine-like components responsible for astrocyte dysfunction, altered neurotransmission (glutamate and GABA tone modulation), energy failure or impaired waist drainage outside the brain.[2]

^{1}H-magnetic resonance spectroscopy (MRS) provides a unique technique able to provide metabolomic spectra in any specific volume of cerebral tissue (voxel). Thus, a specific MRS HE profile has been described by Cordoba *et al.*,[3] which includes an increase in the glutamine/glutamate level and a decrease in myoinositol and choline levels, in compensation for glutamine osmotic power. The availability of higher magnetic fields has enabled researchers to better separate close peaks in the spectra. Thus, Braissant *et al.* provide,[4] in a validated animal model of HE, the biliary duct ligation model,[5] a very precise description of an HE profile and its time-course over several weeks by using a 9.4 Tesla MRI, compared to the classical 1.5 Tesla MRI that has been used in previous studies. By taking advantage of this, the authors were able to describe the sequential abnormalities that appear on the spectra, to separate glutamine from glutamate peaks and to study some other compounds such as ascorbate, which they found decreased in HE. We previously suggested, in a recent metabolomic study of cerebrospinal fluid, that energy failure could participate in HE pathophysiology, but we failed to find any abnormality in ascorbate concentrations.[6] Like metabolomics, MRS could be a useful tool to study HE metabolic pathways involved *in vivo* in humans. Moreover, as opposed to cerebrospinal fluid metabolomics assessment, which is unethical and therefore not feasible, MRS could become a non-invasive surrogate marker for the evaluation of HE treatment strategies, especially if using high field magnets that enable a quantitative assessment of the different peaks. So far, MRS parameters have been shown to be influenced by changes in patient's neurological status[7] and therapeutic strategies, like transhepatic intrajugular portosystemic shunt placement or liver transplantation, for example.[8,9] Currently, MRS is not used as a diagnostic tool for HE in clinical practice, whereas it could be helpful, especially in minimal HE (MHE) where no gold-standard for diagnosis is available.[10]

We report here our real-life experience of MRS in our outpatient clinics, where cirrhotic patients are explored when HE is suspected. MRS were performed on a 3 Tesla MRI and MRS voxels were placed in the *corona radiata*. The final radiological interpretation was reviewed. A post-treatment analysis quantified glutamine, glutamate, N-acetyl-aspartate, choline and myoinositol levels reported to the level of creatine. The majority of patients underwent a clinical examination by a neurologist, psychometric tests (critical flicker frequency and/or psychometric hepatic encephalopathy score) and had their ammonia levels tested. The diagnosis of MHE was made by an adjudication committee made up of 2 experts (DT, NW). Patients in whom consensus could not be achieved were excluded.

Between February 2013 and April 2016, 51 cirrhotic patients were referred to our outpatient clinics to assess the presence of MHE. The etiology of cirrhosis was alcohol 35%, metabolic syndrome 13%, viral 26%, mixed 23%, other 3%. The median model for end-stage liver disease score was 10 [7–12]. Seven patients were excluded because consensus for diagnosis was not reached. In the remaining patients, according to the experts, 50% had an MHE and 50% did not. Among them, 31 underwent brain MRI with MRS; 20 displaying MHE and 11 without. Median age was 60 years (54–62) (Table 1). Whereas T1-weighted hypersignals in both *pallidum* were found in 18 (58%) on MRI, MRS showed an HE profile in 19 (61%). Nineteen (95%) MHE patients had typical MRS HE profiles according to the radiological interpretation. Whereas glutamine/creatine and glutamate/creatine levels were increased in patients with MHE, myoinositol/creatine levels were decreased. Choline/creatine levels were not modified significantly.

Our preliminary results confirm Braissant *et al.*'s results and suggest that MRS could outperform other available tools to diagnose MHE. In the field of multiple sclerosis, major therapeutic advances have been made in the last decades and many others are expected. This progress would not have been possible without the development and validation of a surrogate marker of the disease by brain MRI, *i.e.* the annualized number of new lesions. In addition to its potential diagnostic use, MRS could also be a valuable tool to assess the efficacy of treatments in cirrhotic patients with HE. The availability of such a surrogate marker could boost the development of new therapeutic strategies.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.008.

Keywords: Magnetic resonance spectroscopy; MRI; MRS; Cirrhosis; Hepatic encephalopathy.
Received 9 July 2019; accepted 12 July 2019

Table 1. Baseline characteristics.

	Total population n = 31	MHE n = 20	No MHE n = 11	*p*
Age, years	60 (54–62)	61 (54–64)	56 (54–61)	0.49
Sex ratio, men/women	1.8	1.2	4.5	0.24
Previous medical history				
Ascites, n (%)	22 (71)	15 (75)	7 (63)	0.66
Upper gastrointestinal bleeding, n (%)	10 (32)	5 (25)	5 (45)	0.36
Overt HE, n (%)	15 (48)	9 (45)	6 (55)	0.72
Treatment, n (%)				
TIPS	6 (19)	6 (30)	0 (0)	0.07
Lactulose or rifaximin	14 (45)	12 (60)	2 (18)	0.06
Biology				
Bilirubin, μmol/L	26 (17–39)	27 (21–38)	17 (13–37)	0.19
Albumin, g/L	35 (31–38)	39 (36–40)	32 (28–35)	0.001
Prothrombin time, %	65 (57–80)	61 (57–66)	87 (78–93)	0.008
INR, %	1.3 (1.2–1.5)	1.4 (1.3–1.5)	1.1 (1.1–1.2)	0.007
MELD	10 (7–12)	11 (9–12)	7 (5–10)	0.15
Creatinine, μmol/L	68 (57–83)	62 (57–79)	83 (61–92)	0.17
HE work-up				
Ammonia, μmol/L	57 (44–96)	69 (55–112)	45 (36–54)	0.009
Ammonia ≥50 μmol/L	20 (65)	17 (85)	3 (27)	0.009
CFF, Hz	40.1 (33.4–46.1)	41.2 (33.9–45.4)	37.6 (33.6–46.0)	0.83
MMSE, points	26 (21–30)	24 (21–29)	28 (25–30)	0.54
MOCA, points	23 (20–27)	22 (19–24)	27 (27–29)	0.14
PHES	–2.5 (–2.0 to –4.8)	–3 (–2.0 to –7.0)	–2 (–2.0 to –3.0)	0.76
Brain MRI				
T1 hypersignals of pallidum, n (%)	18 (58)	16 (80)	2 (18)	<0.001
MRS HE spectra, n (%)	19 (61)	19 (95)	0 (0)	<0.001
MRS peaks				
NAA/Cr	1.56 (1.50–1.62)	1.60 (1.53–1.64)	1.51 (1.44–1.55)	0.017
Glu/Cr	0.74 (0.68–0.80)	0.79 (0.72–0.84)	0.66 (0.61–0.68)	0.001
Glx/Cr	0.83 (0.78–0.92)	0.87 (0.82–0.99)	0.78 (0.66–0.80)	0.010
tCho/Cr	0.83 (0.79–0.87)	0.82 (0.78–0.85)	0.86 (0.82–0.98)	0.130
mIns/Cr	0.64 (0.56–0.75)	0.58 (0.53–0.64)	0.77 (0.72–0.93)	0.001

CFF, critical flicker frequency test; Cr, creatine-phosphocreatine; Glu, glutamate; Glx, glutamine + glutamate; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; mIns, myo-inositol; MMSE, mini mental state examination; MOCA, Montreal cognitive assessment; MRS, magnetic resonance spectroscopy; n.a., not applicable; NAA, N-acetyl-aspartate; PHES, psychometric hepatic encephalopathy score; tCho, total choline; TIPS, transhepatic intrajugular portosystemic shunt.

All results are expressed as median and inter-quartile intervals for quantitative variables and as absolute values and percentages for qualitative variables. We compared patients between the 2 groups by using non-parametric tests (Mann-Whitney-Wilcoxon for quantitative variables or Chi-square and Fisher exact tests for qualitative variables).

References

[1] Weiss N, Jalan R, Thabut D. Understanding hepatic encephalopathy. Intensive Care Med 2018;44:231–234. https://doi.org/10.1007/s00134-017-4845-6.

[2] Hadjihambi A, Arias N, Sheikh M, Jalan R. Hepatic encephalopathy: a critical current review. Hepatol Int 2018;12:135–147. https://doi.org/10.1007/s12072-017-9812-3.

[3] Córdoba J, Sanpedro F, Alonso J, Rovira A. 1H magnetic resonance in the study of hepatic encephalopathy in humans. Metab Brain Dis 2002;17:415–429. https://doi.org/10.1023/A:1021926405944.

[4] Braissant O, Rackayová V, Pierzchala K, Grosse J, McLin V, Cudalbu C. Longitudinal neurometabolic changes in the hippocampus of a rat model of chronic hepatic encephalopathy. J Hepatol 2019;71:505–515. https://doi.org/10.1016/j.jhep.2019.05.022.

[5] Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, et al. Review article: the design of clinical trials in hepatic encephalopathy – an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement: Review: ISHEN consensus statement for hepatic encephalopathy trials. Aliment Pharmacol Ther 2011;33:739–747. https://doi.org/10.1111/j.1365-2036.2011.04590.x.

[6] Weiss N, Barbier Saint Hilaire P, Colsch B, Isnard F, Attala S, Schaefer A, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy. J Hepatol 2016;65:1120–1130. https://doi.org/10.1016/j.jhep.2016.07.046.

[7] Shawcross DL. Low myo-inositol and high glutamine levels in brain are associated with neuropsychological deterioration after induced hyperammonemia. AJP Gastrointest Liver Physiol 2004;287:G503–G509. https://doi.org/10.1152/ajpgi.00104.2004.

[8] Rudler M, Weiss N, Perlbarg V, Mallet M, Tripon S, Valabregue R, et al. Combined diffusion tensor imaging and magnetic resonance spectroscopy to predict neurological outcome before transjugular intrahepatic portosystemic shunt. Aliment Pharmacol Ther 2018;48:863–874. https://doi.org/10.1111/apt.14938.

[9] Weiss N, Thabut D. Neurological complications occurring after liver transplantation: role of risk factors, hepatic encephalopathy, and acute (on chronic) brain injury. Liver Transplant 2019;25:469–487. https://doi.org/10.1002/lt.25420.

[10] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatol Baltim Md 2014;60:715–735. https://doi.org/10.1002/hep.27210.

Bertrand Hermann[1]
Marika Rudler[2]
Damien Galanaud[3]
Dominique Thabut[2]
Nicolas Weiss[4,*]

[1]*Sorbonne University, Brain and Spine Institute – Institut du Cerveau et de la Moelle Epinière, ICM, Inserm U 1127, CNRS UMR 7225, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Charles Foix Hospital, Department of Neurology, Neurological Intensive Care Unit, Paris, France*
[2]*Sorbonne Université, Brain Liver Pitié-Salpêtrière (BLIPS) Study Group, INSERM UMR_S 938, Centre de recherche Saint-Antoine, Maladies métaboliques, biliaires et fibro-inflammatoire du foie, Institute of Cardiometabolism and Nutrition (ICAN), Assistance Publique – Hôpitaux de Paris, Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Service d'hépato-gastroentérologie, Service d'hépatologie, Unité de Soins Intensifs d'Hépato-gastroentérologie, Paris, France*
[3]*Sorbonne Université, Brain Liver Pitié-Salpêtrière (BLIPS) Study Group, Assistance Publique – Hôpitaux de Paris, Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Service de neuroradiologie, Paris, France*
[4]*Sorbonne Université, Brain Liver Pitié-Salpêtrière (BLIPS) Study Group, INSERM UMR_S 938, Centre de recherche Saint-Antoine, Maladies métaboliques, biliaires et fibro-inflammatoire du foie, Institute of Cardiometabolism and Nutrition (ICAN), Assistance Publique – Hôpitaux de Paris, Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Département de Neurologie, Unité de réanimation neurologique, Paris, France*
*Corresponding author. Address: Sorbonne Université, Unité de réanimation neurologique, Département de neurologie, Groupe hospitalier Pitié-Salpêtrière Charles Foix, Assistance Publique-Hôpitaux de Paris, 47-83 boulevard de l'hôpital, 75013 Paris Cedex 13, France; Tel.: +33(0)1.42.16.27.70, Fax: +33(0)1.42.16.19.89.
E-mail address: nicolas.weiss@aphp.fr

Reply to: "Magnetic resonance spectroscopy: A surrogate marker of hepatic encephalopathy?"

To the Editor:

We have read the Letter by Hermann *et al.*[1] in detail in which they summarize their ^{1}H-MRS findings in a cohort of adult patients with cirrhosis. Their study suggests that abnormal ^{1}H-MRS using clinically available magnets is highly predictive of abnormal psychometric tests in a population with compensated liver disease (median model for end-stage liver disease score of 10). What's more, an abnormal spectrum appeared to be more predictive of HE than the hallmark finding of hyperintense signal in the T_1 weighted sequences. We are confident that this interesting clinical observation is auspicious for forthcoming studies using higher resolution spectroscopy, following the advent of 7 Tesla magnets in the clinical arena, which will lead to the detection of additional metabolites, as shown by our pre-clinical study performed at 9.4 Tesla.[2] Finally, a series of consensus recommendations on clinical ^{1}H-MRS are now available,[3,4] recommending appropriate methodology to improve the quality of future MRS studies and increase MRS standardization, with the final aim of improving the clinical utility of MRS.

Financial support

Financial support was provided by the SNSF project no 310030_173222/1, the EU: FP7-PEOPLE-2012-ITN project 316679 TRANSACT and by the CIBM (UNIL, UNIGE, HUG, CHUV, EPFL, as well as the Leenaards and Jeantet Foundations), the CHUV and the HUG.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.003.

References

Author names in bold designate shared co-first authorship

[1] Hermann B, Rudler M, Galanaud D, Thabut D, Weiss N. Magnetic resonance spectroscopy: a surrogate marker of hepatic encephalopathy?. J Hepatol 2019;71:1055–1057.
[2] **Braissant O**, **Rackayová V**, Pierzchala K, Grosse J, McLin V, Cudalbu C. Longitudinal neurometabolic changes in the hippocampus of a rat model of chronic hepatic encephalopathy. J Hepatol 2019;71:505–515. https://doi.org/10.1016/j.jhep.2019.05.022.
[3] Oz G, Alger JR, Barker PB, Bartha R, Bizzi A, Boesch C, et al. Clinical proton MR spectroscopy in central nervous system disorders. Radiology 2014;270:658–679. https://doi.org/10.1148/radiol.13130531.
[4] Wilson M, Andronesi O, Barker PB, Bartha R, Bizzi A, Bolan PJ, et al. Methodological consensus on clinical proton MRS of the brain: review and recommendations. Magn Reson Med 2019;82:527–550. https://doi.org/10.1002/mrm.27742.

Valérie A. McLin[1]
Olivier Braissant[2]
Cristina Cudalbu[3,*]
[1]*Swiss Pediatric Liver Center, Department of Pediatrics, Gynecology and Obstetrics, University Hospitals Geneva, and University of Geneva Medical School, Switzerland*
[2]*Service of Clinical Chemistry, University of Lausanne and University Hospital of Lausanne, Lausanne, Switzerland*
[3]*Centre d'Imagerie Biomedicale (CIBM), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland*
Corresponding author. Address: Centre d'Imagerie Biomedicale (CIBM), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland. Tel.: +41216937685.
E-mail address: cristina.cudalbu@epfl.ch