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ORIGINAL ARTICLE

Cerebral water content mapping in cirrhosis patients with and without manifest HE

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Abstract

Hepatic encephalopathy (HE) is a frequent and debilitating complication of cirrhosis and its pathogenesis is not definitively clarified. Recent hypotheses focus on the possible existence of low-grade cerebral edema due to accumulation of osmolytes secondary to hyperammonemia. In the present study we investigated increases in cerebral water content by a novel magnetic resonance impedance (MRI) technique in cirrhosis patients with and without clinically manifest HE**.** We used a 3 T MRI technique for quantitative cerebral water content mapping in nine cirrhosis patients with an episode of overt HE, ten cirrhosis patients who never suffered from HE, and ten healthy aged-matched controls. We tested for differences between groups by statistical non-parametric mapping (SnPM) for a voxel-based spatial evaluation. The patients with HE had significantly higher water content in white matter than the cirrhosis patients (0.6%), who in turn, had significantly higher content than the controls (1.7%). Although the global gray matter water content did not differ between the groups, the patients with HE had markedly higher thalamic water content than patients who never experienced HE (6.0% higher). We found increased white matter water content in cirrhosis patients, predominantly in those with manifest HE. This confirms the presence of increasing degrees of low-grade edema with exacerbation of pathology. The thalamic edema in manifest HE may lead to compromised basal ganglia-thalamo-cortical circuits, in accordance with the major clinical symptoms of HE. The identification of the thalamus as particularly inflicted in manifest HE is potentially relevant to the pathophysiology of HE.

Keywords Liver cirrhosis · Hepatic encephalopathy · Absolute free water content · Magnetic resonance imaging · Cerebral edema

Abbreviations

HE Hepatic encephalopathy
CRT continuous reaction time
CSF ventricular cerebrospinal fluid

Introduction

Hepatic encephalopathy (HE) represents a wide spectrum of neurological and neuropsychological symptoms. The

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symptoms may result from astrocyte swelling due to a shift in the distribution of macromolecules secondary to hyperammonemia and accompanied by low-grade cellular brain edema (Grover et al. 2006; Bernal et al. 2007; Haussinger et al. 2000; Rangroo Thrane et al. 2013). Brain edema may become evident in acute liver failure and lead to fatally increased intracranial pressure (Clemmesen et al. 1999). In patients with cirrhosis and HE, the changes are subtle and there are usually no clinical signs of brain edema. Thus, the presence of increased brain water content in cirrhosis is not straightforward to identify, and the matter remains an issue of controversy. This is caused by a lack of appropriate methods for in vivo use in humans. Magnetic resonance imaging (MRI) is often used in attempt to non-invasively assess brain water content in HE studies (Córdoba et al. 2001; Rovira et al. 2008). However, there is no generally accepted method for analyzing and interpreting the MRI findings. Several approaches, such as Magnetization Transfer (MT) imaging, fast fluid-attenuated inversion recovery (FLAIR) and diffusion weighted MR imaging (DWI) (Córdoba et al. 2001; Rovira et al. 2008; Rai et al. 2015; Chen et al. 2015) are to some extent sensitive to changes in brain tissue water, but all lack specificity. Brain MRI studies of patients with HE (Tao et al. 2013) suggest regional changes in intra- or extracellular volume, but do not allow assessment of brain water content.

The recent introduction and establishment of a new MRI sequence (Neeb et al. 2006, Abbas et al. 2015) may render progress in the field possible. The technique is based on the estimation of proton density corrected for field homogeneity, T2* decay, T1-saturation effect, correction of residual non-uniformity, and finally normalization to the ventricular cerebrospinal fluid (CSF) signal. Using this method, the water molarity (mol/L) of the tissue, expressed as a percentage of pure water molarity, is obtained. This method is much more specific than previously applied techniques for quantitation of changes in water content in brain tissue (Neeb et al. 2006; Abbas et al. 2015) The method's advantages are proven in kidney failure patients with large fluid movements due to hemaodialysis (Reetz et al. 2015).

The method has also been applied to cirrhosis patients with clinically undetectable so-called minimal, or low-grade HE, and an increase in cerebral white matter water content was suggested (Shah et al. 2008). However, it remains uncertain if this finding is present in patients with clinically manifest HE, and such knowledge is important for the understanding of the role of brain water content in HE.

In the current study, we investigated whether cirrhosis patients with clinically manifest HE display increased brain water content compared to mentally unimpaired cirrhosis patients and healthy control persons.

Materials and methods

Ethics

The study was approved by the research ethics committee of Region Midtjylland and conducted in agreement with the Helsinki declaration. All participants gave informed consent prior to the study. Next of kin and either a general practitioner or a Medical Public Health Officer gave written surrogate consent for patients who were rendered temporarily incapacitated because of HE.

Participants

We studied ten patients with cirrhosis (cirrhosis group, all alcohol related), clinically stable at the time of the enrollment and with no history or signs of HE or other neuropsychiatric impairment. We also studied nine patients with cirrhosis (alcohol $n = 7$, viral $n = 2$) and clinically manifest, ie. West Haven grade HE 2 or above, type C HE (HE group). Ten healthy persons served as controls. HE precipitating factors were infection ($n = 3$), bleeding ($n = 2$), electrolyte disorder ($n = 4$), and in one case unidentified. All patients were scanned within one day of admission; two HE patients were scanned again after full recovery. The HE patients received standard supportive medical therapy, oral administration of lactulose, and no other anti-HE treatment. The patients were hemodynamically stable and did not require respiratory or circulatory support. They were recruited from the Department of Hepatology and Gastroenterology, Aarhus University Hospital, Denmark. The ten age-matched healthy volunteers were recruited amongst relatives and hospital staff. Exclusion criteria in all groups were neurological or psychiatric disability or brain anomalies, and use of CNS-active medications such as benzodiazepines, anti-epileptics, or antidepressants. Patients and controls underwent a detailed standard clinical examination on the morning before the MRI studies. In addition, the mentally unimpaired patients underwent a continuous reaction time (CRT) test (Elsass and Hartelius 1985; Lauridsen et al. 2017) to exclude minimal HE. Blood was drawn for routine hematology and biochemistry before the MRI scans. Due to interference with bilirubin, measurement of ammonia was not possible in 3 patients. Two patients received antibiotics to control their infection.

MRI acquisition and quantitative analysis

Cerebral MRI acquisitions were performed on a 3 Tesla Tim Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany) at the Center of Functionally Integrative Neuroscience, Aarhus University, Denmark. Quantitative maps of cerebral free water content were acquired using a method first described by Shah and colleagues (Neeb et al. 2006; Shah et al. 2008) and optimized for acquisition at 3 Tesla (Abbas 2015). The ventricular cerebrospinal fluid was used for

normalization. The total acquisition time for the protocol was fourteen minutes. The free water content was estimated using in-house MATLAB algorithms, (MATLAB 2016, The MathWorks, Inc., Natick, Massachusetts, United States). Further pre-processing was performed using the statistical parametric mapping toolbox, SPM12, v6685 (Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The resulting maps were segmented into binary images representing grey matter, white matter, cerebrospinal fluid, skull, and tissue/meninges for each individual participant. 'Skull stripping' was performed and the soft tissue free water content maps were normalized to a standard human brain template (2 mm isotropic MNI152 T_1–weighted).

Statistical inference

Histograms of all free water content voxel values were constructed in each brain map. Average histograms were calculated and the distribution of free water content in the study groups was compared. The maps were subjected to a voxel-based non-variance smoothed analysis with the Statistical Non Parametric Mapping toolbox (SnPM v13.01, http://www.fil.ion.ucl.ac.uk/spm/snpm). The statistical maps were superimposed on single subject human brain templates (SPM MNI T_1 single subject template, 2 mm isotropic) for anatomical reference.

Results

Participants

The clinical characteristics are summarized in Table 1. The mentally unimpaired patients had normal CRT test results. As expected, the HE patients had a lower prothrombin index ($P < 0.05$), higher bilirubin concentration ($P < 0.05$), higher Child-Pugh scores ($P < 0.05$), lower hemoglobin ($P < 0.05$) and higher arterial blood ammonia ($P < 0.05$) than the cirrhosis patients with no history of HE.

Brain tissue water content

The average spatial free water maps and global histograms for the study groups are illustrated in Fig. 1a. The voxel-based statistics (SnPM) showed significantly higher water content in white matter in the patients with manifest HE compared to the non-HE patients. These in turn had higher water content in localized white matter regions compared to the controls (Fig. 1b). The same pattern was present in the histograms (Fig. 1a), where a white matter water peak was seen in the control histogram (indicated by arrowhead), which is less apparent in the cirrhosis patient histogram and absent in the HE histogram, reflecting the increasing white matter free water content gradient from healthy control to cirrhosis patient to HE patient. The patients with manifest HE had significantly higher water content in the thalamus compared to the non-HE cirrhosis patients (Fig. 1b).

We used individually defined regional masks and found average white matter brain water content values of 73.0% ± 3.6% in the patients with manifest HE, 72.6% ± 1.9% in the non-HE patients, and 71.3% ± 1.3% in the controls. The global gray matter water content did not differ between the groups. However, the patients with manifest HE had higher thalamic water content (85.8% ± 3.0%) than the non-HE patients (81.0% ± 3.0%), an effect not apparent in any other brain region.

In both patients studied longitudinally, global white matter and thalamic water content decreased after recovery of the acute HE episode (Fig. 2).

Table 1 Patient characteristics

		Cirrhosis patients	
	Controls	Cirrhosis patients Never HE	Type C episode of manifest HE
Number of patients	10	10	9
Female/male	5/5	2/8	1/8
Age [years]	66(54–76)	53 (41–68)	58 (20–75)
Bilirubin	–	25 ± 5	332 ± 126*
New Haven encephalopathy grade	–	Unimpaired	II:4 III:3;IV:2
Child-Pugh class	–	A: 2; B: 8	A: 0; B: 2; C: 7
Prothrombin index	–	0.57 ± 0.04	0.17 ± 0.04*
CRT index	–	2.2 (1.9–2.6)	–
Hemoglobin [mmol/L]	–	8.7 ± 0.5	5.9 ± 0.4*
Arterial ammonia [μmol/L]	–	31 ± 7	120 ± 16*
Albumin [gl/dL]	–	36 ± 2	24.2 ± 1.4*

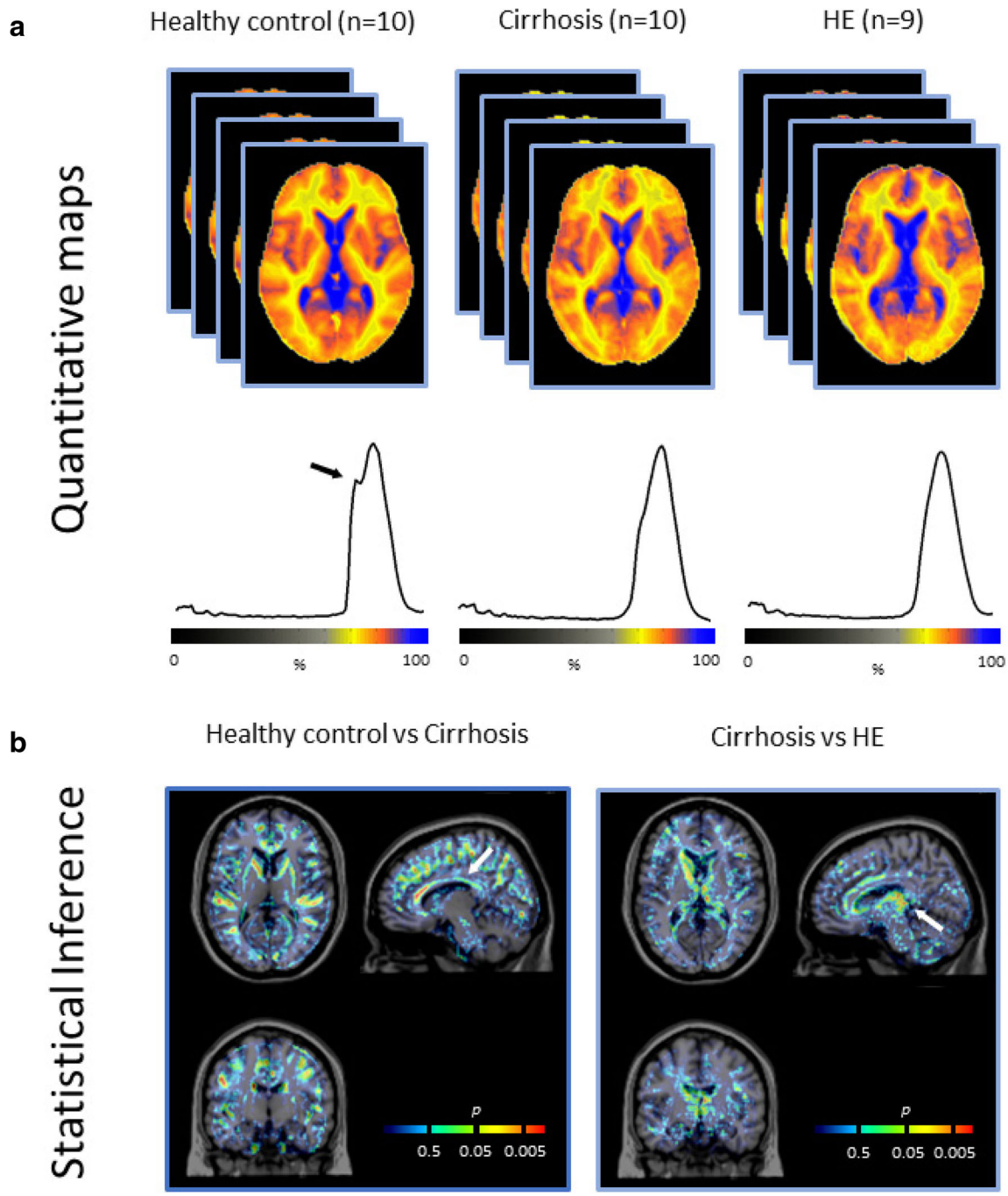

Fig. 1 Cerebral Water Content. **a** Brain axial slices of water content maps obtained from averages of healthy controls, cirrhosis patients and cirrhosis patients with HE (Top row, from left to right). Distribution of brain absolute free water content is shown as mean value histograms (Middle row). The shoulder of the peak in the control (see arrowhead, left) histogram represents white matter pixels and the peak itself represents grey matter pixels since grey matter has higher water content than white matter. There is higher white matter water content in both groups of cirrhosis patients compared to the control group (~1%). No differences are detected in gray matter. Cirrhosis patients have higher water content than controls, and cirrhosis patients with overt HE have higher levels than patients with no history of HE. The color bars represent the water content in percent. **b** Differences between healthy control and cirrhosis patient groups were assessed using statistical non-parametric mapping and are shown as an overlaid *p* value map on an anatomic template. Analyses of quantitative water content revealed increases in predominantly white matter regions in cirrhosis patients compared to controls (see arrow, left panel, corpus callosum), and in the thalamus (see arrowhead, right panel, thalamus) and white matter regions in the cirrhosis patients with manifest HE compared to cirrhosis patients without HE. There is a large increase in the thalamic water content in the cirrhosis patients with HE compared to those without HE, represented by a white arrow. The color bar displays the *p*-values on a logarithmic scale

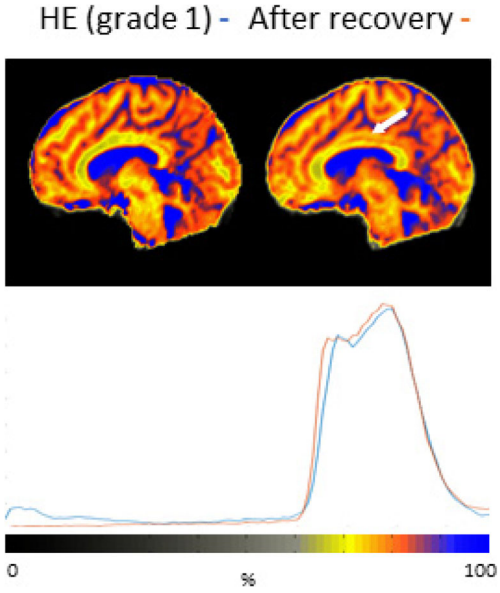

Fig. 2 Water content during HE and after recovery. Sagittal slices of water content maps in a 50-year-old cirrhosis patient with HE (grade 1) (top, left) and four months after successful recovery (top, right). Note the decreases in the corpus callosum (which is a high density white matter structure; see arrow, right panel). Histograms (bottom) illustrating the distribution of water content reveal decreased white matter water content (1.4%) as shown by the broadening of the peak in the recovery state compared with the HE state. The color bars represent the water content in percent ranging from zero to 100 %

Discussion

The key findings of the present study are that the cirrhosis patients with manifest HE had higher white matter water content, and particularly higher thalamic water content, than the non-HE patients who in turn had higher white matter water content than the healthy controls. Patients with manifest HE have not previously been studied by the MRI brain water mapping method.

The higher white matter water content present in HE patients is in accordance with the previous study by Shah et al. (2008) This group also found and an association between the presence of HE and increased water content in the frontal and occipital white matter, the globus pallidus, the anterior limb of the internal capsule and the putamen, but they did not identify the marked involvement of the thalamus described in the current study. One plausible reason for this discrepancy is that they studied only patients with discrete or minimal HE whereas the patients included in the present study had manifest HE with significantly increased plasma ammonia levels Thus, the increased thalamic water content may be a trait of severe HE, possibly related to their fourfold higher ammonia concentration.

Thalamic swelling or edema likely has widespread consequences because the thalamus plays a central role in attention, arousal, sleep, and circadian rhythms (Filley 2002; Gosseries et al. 2011a, b) and serves as a relay station of sensory impulses to cortical cognitive functions (Weissenborn et al. 2005). The normal functions of the thalamic circuits are compromised by edema and ultimately result in coma Filley 2002; Weissenborn et al. 2005). Such functional deficits to a large degree appropriately describe the complex clinical picture of manifest HE.

In support, an increased thalamic volume was observed in most (Chen et al. 2012, Zhang et al. 2012) though not all (Guevara et al. 2011), voxel-based morphometry studies of HE patients, and our data suggest this to be due to increased water content. This is mechanistically supported by data showing an increased thalamic uptake of ammonia, which may lead to osmolytic water accumulation (Ahl et al. 2004).

It is a strength of the current study and an expansion of earlier MRI brain water mapping studies (Shah et al. 2008; Tao et al. 2013; Abbas et al. 2015), that we included cirrhosis patients with no history of HE. Such mentally unimpaired cirrhosis patients already had increased white matter water, but not thalamic swelling. This seems to indicate that brain water increase is an early finding of cirrhosis and that the degree and localization of the water accumulation is most relevant to the emergence of manifest HE. The cerebral water increase may therefore represent a state that conditions the patients for developing HE.

This line of thought is corroborated by the two patients imaged in a longitudinal design that in parallel recovered from HE and had reduced white matter and thalamic water content. In accordance, albeit more indirectly, it is in support that MRI magnetization transfer ratios, that may be taken as a proxy marker of brain water, are described to normalize after liver transplantation of HE patients (Rovira et al. 2007).

It is a possible source of bias that we dimensioned the brains from all our study groups into a common atlas. This may be less precise because some patients might have brain atrophy with more CSF space (Miese et al. 2009; Zeneroli et al. 1991). We therefore normalized to CSF space and smoothed the images when testing different tissues across anatomical boundaries. The findings relating to the thalamus are not sensitive to this issue because the thalamus is a relatively large region and the majority of its voxels are not close to the ventricles. An additional limitation is the small number of patients. This was a result of both the ethical and logistic difficulties in conducting such studies while the patients had manifest HE requiring consent from next of kin. Furthermore, the strict recruitment criteria limited the number of patients, as did their high occurrence of co-morbidities prohibiting MRI. We attempted to counteract this limitation by using advanced permutation theory for statistical inference.

Conclusion

The patients with manifest HE had higher brain white matter water accumulation compared to non-HE cirrhosis patients, and their thalamus was particularly affected. Also the non-HE patients had a lesser degree of white matter water accumulation, but without the thalamic finding. Our data are in accordance with the theories of the emergence of HE being related to increasing brain osmolytic water accumulation. This phenomenon, most pronounced for the thalamic region, may explain several of the characteristic mental impairments of manifest HE.

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Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest related to publication of the data in this manuscript.

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