Quantitative Measurement of Absolute Water Content in Hepatic Encephalopathy

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INTRODUCTION

Hepatic encephalopathy (HE) is a frequent neuropsychiatric complication in patients with liver cirrhosis and is usually classified in 5 stages. The diagnosis of overt HE (grade I-IV) is based on clinical assessment while the detection of subclinical forms of the disease (mHE) remains a major diagnostic challenge because of the low specificity of currently used neuropsychiartric testing procedures [1]. Results from *in vitro* studies and animal models suggest that HE is a consequence of astrocyte swelling in the brain which is mediated by cytokines, hyponatremia, benzodiazepines and neurotoxins such as NH_3 resulting in a cerebral oedema [2]. It was also proposed that the amount of swelling and the resulting brain oedema correlates with disease grade [3]. Currently, no method has quantitatively measured the presence of brain oedema *in vivo*, its real extent or the brain regions affected.

We present results from the measurement of localised absolute water content in a cohort of patients with different severities of hepatic encephalopathy as well as normal volunteers based on the combination of two fast, multi-slice and multi-time-point sequences QUTE-EPI and TAPIR (T_1 mApping with Partial Inversion Recovery) for mapping the T_2^* and T_1 relaxation times, respectively [4][5][6]. The resulting localized cerebral water content can be determined with an error <2% in approximately 21 minutes, incorporating all relevant correction factors [7], demonstrating the clinical usefulness of the method for absolute water content mapping in hepatic encephalopathy.

METHODS

T_2^* was measured using the QUTE-EPI sequence with the following parameters: TR=138ms; TE=4ms; α=90°; 17 slices; 64 time points; echo spacing=2ms; matrix size=256^2; FOV=220mm; slice thickness=5mm; rf-spoiling employed; 10 preparation scans. T_1 mapping was performed using TAPIR. The following parameters were employed: TR=15ms; TE_1: TE_2: TE_3=2.8: 5.1: 7.5ms; α=25°; 18 slices; 20 time points; matrix size=256^2; FOV=220mm; slice thickness=5mm; sequential excitation; delay time τ=2s. The first point for the first slice on the recovery curve was sampled 10ms after inversion. Inefficiencies of the inversion pulse were corrected using the procedure described in [8]. The T_2^* relaxation curve was extrapolated to an echo time TE=0 to extract the parameter M_0 (tissue). An absolute measure of water content was obtained by placing a reference probe containing doped water within the FOV thereby relating the parameter M_0 (tissue) to M_0 (reference). Corrections for temperature differences between tissue and the reference probe, T_1 saturation as determined by TAPIR, receiver coil imperfections, inversion-pulse inefficiency and local flip angle miscalibrations were included. Incorporating all correction factors, the spatial water content in the human brain can be determined in approximately 21 minutes with a precision of >98% including statistical and systematic error components [7].

The method was employed in a cohort of 23 patients suffering from HE with varying clinical grade as well as 32 healthy controls. The HE cohort was comprised of 10 HE-0, 6 mHE, 4 HE-I and 3 HE-II patients. White matter and cortical grey matter were segmented based on quantitative T_1 information acquired with TAPIR. Voxels with T_1 in a range of [450ms, 650ms] where considered to be white matter while grey matter was segmented by constraining the longitudinal relaxation time to [1000ms, 1150ms]. Age- and gender-related effects on cerebral water content were determined based on the results from the 32 normal healthy volunteers from another study. The patient and the control data here were thereby corrected. Correlation between MR-measured quantitative water content in cortical grey and white matter and results from neuropsychiatric tests as well as disease grade was performed to search for brain regions with elevated water content and for their correlation with HE severity.

RESULTS AND DISCUSSION

Fig 1a shows the water map from a 65 year old patient suffering from HE grade II. A significant correlation between HE severity and water content in white matter is demonstrated by Fig 2a. This is, to our knowledge, the first direct and unambiguous and quantitative demonstration *in vivo* of the association between hepatic encephalopathy severity and increased water content in white matter. In contrast, water content in cortical grey matter seems to increase only in late-stage disease as shown in fig. 1c.

These results clearly demonstrate that quantitative mapping of water content *in vivo* is feasible with high precision in clinically-relevant measurement times. A study, involving a larger group of HE patients of varying disease grade, is currently underway to enhance the statistical significance of the current results.

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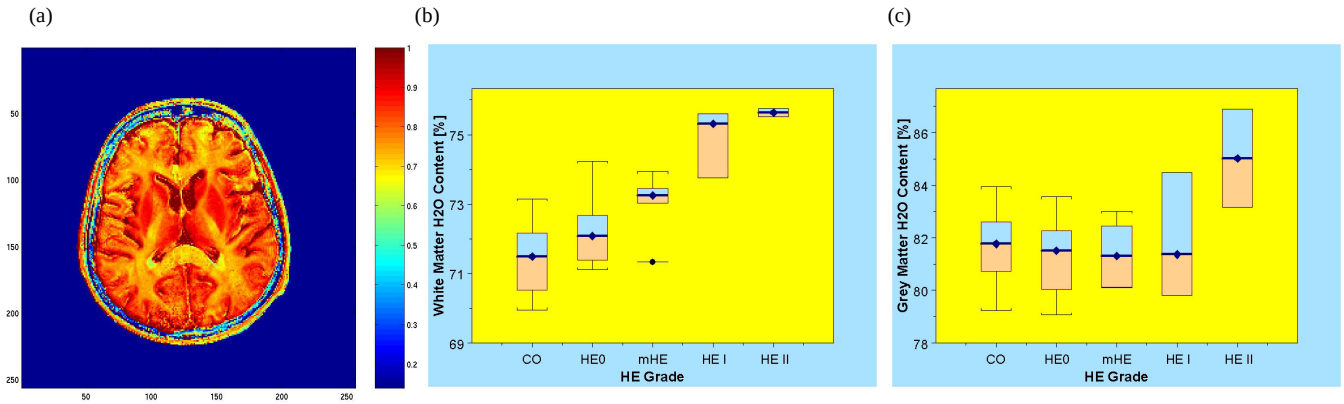

Fig 1: Representative cerebral H_2O content map from a HE grade II patient. (b) Box-Whisker plot showing the changes of white matter H_2O content with disease grade. "CO" represents the healthy control group. (c) same as for (b), but for cortical grey matter.