Subclinical Hepatic Encephalopathy in Children Studied by in vivo ^{1}H NMR Spectroscopy at 4 Tesla

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INTRODUCTION

Hepatic encephalopathy (HE) is a serious neuropsychiatric condition of both acute and chronic liver failure accompanied by metabolic alternations in the brain (1) that can be treated by liver transplantation. Subclinical HE is difficult to diagnose in children with liver disease. MR techniques were used extensively in HE (2-5). The aim of this study was to investigate the potential of high field *in vivo* ^{1}H NMR spectroscopy for the assessment of the status of the subclinical HE in children.

METHODS

Eight pediatric liver transplant candidates (3 female, 5 male, 1.5 – 15 years old) with unknown status of HE were investigated using neurological and neuropsychological testing (attention, cognitive, visual perception), blood analysis for ammonia, and *in vivo* ^{1}H NMR spectroscopy. Four of them were studied also after liver transplantation. All NMR measurements were performed on a 4 T Varian/Siemens system using short echo-time STEAM as previously described (6). All 1st- and 2nd-order shims were adjusted by FASTMAP (7). Metabolite concentrations were quantified using LCModel with macromolecules included in the basis set (8).

RESULTS AND DISCUSSION

Compared to control subjects, the pre-transplant pediatric candidates had altered neurochemical profile (Fig. 1 and 2). The most pronounced changes included increase of Gln and the decrease of Ins and NAA, in agreement with the literature (2-5), with a substantial change in the [Glu]/[Gln] ratio ($p < 0.0001$). Glutamine concentration was elevated by more than 100% (arrow in Fig. 1), whereas the commonly measured Glx (Gln + Glu) increased by only 33%. Reliable discrimination of Gln and Glu (Cramer-Rao lower bounds < 10%) resulted from increased spectral resolution at 4 T (9). In addition, increased levels of Glc and GSH were observed. No significant correlation was found between [Glu]/[Gln] and either blood ammonia or neurological and neuropsychological tests, which may be due to the difficulty of applying some of these tests in children. The scatter of the Gln measurement in HE patients (4 – 8 µmol/g) was significantly higher than the precision of the NMR measurement, reflecting biological variation in HE. This indicates the potential for grading subclinical HE in children at 4 T. Liver transplantation reversed the markers of HE closer to the normal values (not shown). However, the post-transplant concentration of Gln remained significantly higher than in normal adult brain, indicating a slower than expected reversal of the effects of liver hypofunction on the neurochemistry.

In conclusion, high-field *in vivo* ^{1}H NMR spectroscopy can provide a precise assessment of the subclinical HE status in children. The dynamic range of concentration changes of Gln and Ins should allow grading of subclinical HE, which may aid in determining the optimal therapy for pediatric patients awaiting liver transplantation.

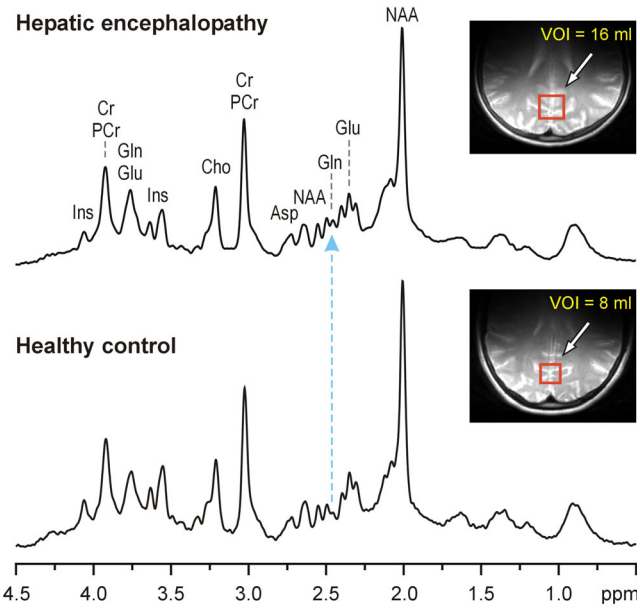

Fig. 1 *In vivo* ^{1}H NMR spectra from the brain of a control and a HE patient (STEAM, TE = 4 ms, TR = 4.5s, NT = 160). The Gln concentration in the patient was 4.9 ± 0.2µmol/g, clearly outside the 95% confidence interval of controls. Insets: RARE images with the size and location of the VOI in occipital lobe.

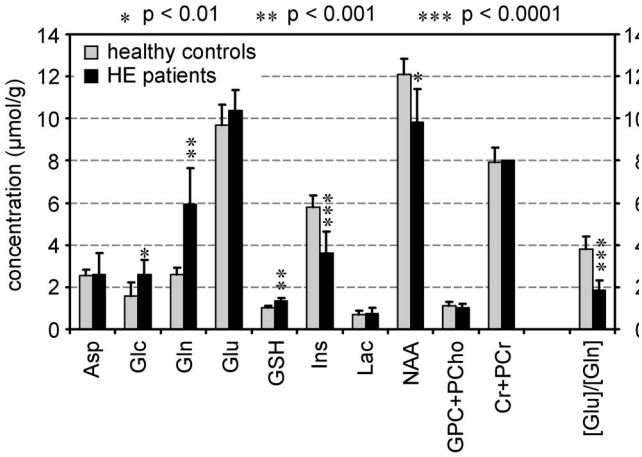

Fig. 2 Concentrations of brain metabolites in the occipital lobe of healthy subjects (n = 8, averaged age ± SD: 25 ± 7) and pre-transplant patients with hepatic encephalopathy (n = 10, referenced to the total creatine of 8 µmol/g). Error bars indicate SD.

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