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# Viability assessment of magnetic resonance spectroscopy for the detection of minimal hepatic encephalopathy severity

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ABSTRACT

*Objective:* To evaluate regional cerebral metabolic changes in minimal hepatic encephalopathy (MHE) patients using magnetic resonance spectroscopy (MRS) in 3T scanner.
*Materials and methods:* This study comprised 30 cirrhotic patients with MHE, 29 cirrhotic patients without MHE and 30 healthy volunteers. Single-voxel proton MRS data in the anterior cingulate cortex (ACC) and basal ganglia were acquired using a 3-T scanner. The concentrations of *N*-acetylaspartate (NAA), mI (myo-inositol), glutamate (Glu), glutamine (Gln) and creatine (Cr) were obtained by LC-model software. Statistical analysis was performed to evaluate the differences between the three groups.
*Results:* There was a significant increase in Glu for the cirrhotic patients, particularly the MHE patients. There was an elevation of Gln in the cirrhotic patients, but not in all cirrhotic patients or controls. There was a significant decrease in mI for the cirrhotic patients, but no significant difference between the two cirrhosis groups. There was no significant difference in NAA between the three groups.
*Conclusions:* MRS using a 3-T MR scanner could detect cerebral metabolic changes in cirrhotic patients with MHE. Glu levels were elevated in cirrhotic patients with MHE; Glu levels could be used as a sensitive indicator to evaluate the severity of MHE in patients with cirrhosis.


## 1. Introduction

Minimal hepatic encephalopathy (MHE) is characterized by the presence of cognitive impairment on psychometric testing and/or the slowing of electroencephalographic (EEG) mean cycle frequency in the absence of any clinically overt signs. This condition is frequently seen in patients with cirrhosis [1]. Hepatic encephalopathy (HE) syndrome is essentially a neuropsychiatric condition and is therefore traditionally diagnosed by neuropsychological tests, which are not specific and do not reveal the underlying pathology [2]. Early diagnosis of MHE might be crucial considering the fact that after a follow-up period of three years, around 50% of cirrhotic patients with MHE present with clinically overt HE, compared with only 8% of patients without MHE [3]. This underscores the prognostic significance of MHE, and is likely to impact on the quality of life of these patients [1].

The pathophysiology, natural history, and prognosis of cirrhosis-associated neuropsychiatric deficits are not fully understood, and the data on this issue are controversial [4]. Recent studies have shown that these deficits are associated with changes in metabolic brain patterns, which may be reversed by a reduction in blood ammonia level [3]. However, long-term persistence of these symptoms following liver transplantation has been reported, and it is suggested that this disorder is neurodegenerative in nature [3].

Adequate clinical neuropsychiatric evaluation of these patients remains difficult because neuropsychiatric symptoms associated with low grade encephalopathy are multiform and sometimes subtle. This problem is further exacerbated in the case of MHE, for which patients only demonstrate deficits on neuropsychological tests [5]. Furthermore, these tests can be subject to confounding factors such as age, superimposed mood disorders, and level of education [6]. Therefore, there has been increasing interest in the use of noninvasive imaging techniques, such as magnetic resonance spectroscopy (MRS), to assist in the evaluation of MHE [7].

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$H^1$-MRS has been used extensively to evaluate brain changes in cirrhosis patients [6,8]. In patients with HE, it has been observed that myo-inositol (mI) was reduced with increasing concentrations of glutamate/glutamine (Glx) [9]. Glutamate (Glu) is an excitatory neurotransmitter, which is considered to play a role in the pathophysiology of HE [10]. Previous studies have reported changes in Glx, rather than individual changes in Glu and glutamine (Gln) [8]. Since the blood–brain barrier (BBB) is permeable to Gln, which is not a neurotransmitter, there is uncertainty regarding the results of the studies that focused on Glx. In this study, we conducted MRS using a high-magnetic field MR (3T) to separate Glu from Gln, and analyzed the data to determine the correlation between NAA, Cr, mI, Gln, and Glu levels and the pathophysiology of HE.

## 2. Material and methods

### 2.1. Subjects

The subjects were divided into three groups. Group I: 33 patients diagnosed with liver cirrhosis with MHE; group II: 30 patients diagnosed with liver cirrhosis without HE; and group III: 30 healthy controls.

The patients were clinically evaluated during their initial assessment. The cognitive evaluation included a psychiatric history and the mini-mental status examination (MMSE). Patients scoring less than 24 on the MMSE were classified as cognitively impaired and were excluded from the study [3]. Liver cirrhosis was diagnosed using general evaluation methods, such as imaging techniques (e.g., abdominal ultrasonography, computed tomography), histological examination and blood biochemical data. The exclusion criteria included: claustrophobia during MR examination; age of less than 18 or more than 75 years; active alcoholism during the 3 months before the study; HE grades of II–IV; a Child–Pugh score (which assesses the severity of liver disease) of C; additional neurological or psychiatric disease; treatment with psychotropic drugs or other drugs known to alter neuropsychological function; gastrointestinal bleeding or infection within 1 week before the study; and previous treatment with shunt procedures.

Control subjects were recruited through advertisements. None of the controls had any history of neurological or psychiatric illness, metabolic disorders, alcohol or drug abuse, head injury or liver disease. All patients underwent a detailed clinical assessment, including a neurological examination.

Written informed consent was obtained from each participant included in this study and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved by the Ethics Committee of the local Institutional Review Board.

### 2.2. Clinical neuropsychological tests

A number connection test type A (NCT-A) and a digit symbol test (DST) were performed, as recommended by the international HE working party at the 11th World Congress of Gastroenterology, Vienna, 1998 [1]. Results were considered abnormal when the test score was 2 standard deviations above or below the age- and education-matched controls [11]. Patients with abnormal NCT-A and/or DST results, but without overt clinical HE, were classified as having MHE [1].

### 2.3. Laboratory examination

Blood biochemistry tests, including prothrombin time, protein metabolism tests (e.g., total protein, globulin, albumin, the ratio of albumin and globulin), bilirubin metabolism tests (e.g., total bilirubin, direct bilirubin, indirect bilirubin), glutamic pyruvic transaminase and glutamic oxaloacetic transaminase, were performed within one week prior to MR scanning for all patients. The above-mentioned tests were used to calculate the Child–Pugh score to assess the severity of liver disease [11]. Venous blood ammonia tests were also conducted.

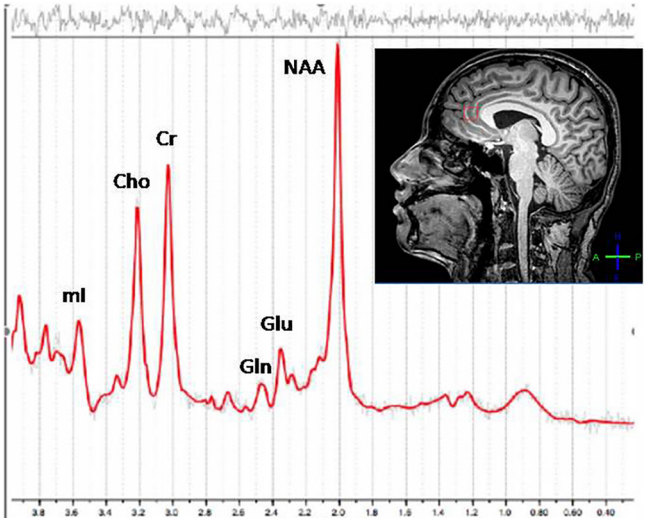


**Fig. 1.** Metabolite changes in the ACC for the cirrhotic patients with MHE (49-year-old, male). It was revealed that Glu was present at 2.35 ppm, Gln at 2.45 ppm, mI at 3.55 ppm, Cr at 3.02 ppm, and NAA at 2.01 ppm.
ACC, anterior cingulate cortex; MHE, minimal hepatic encephalopathy; Glu, glutamate; Gln, glutamine; mI, myo-inositol; Cr, creatine; NAA, *N*-acetylaspartate.

### 2.4. MR examination

In vivo single-voxel MRS was performed using a Philips 3-T MRI system (Intera Achieva 3.0T/Quasar, Philips Medical System, The Netherlands) equipped with an 8-channel phase coil. Anatomical T1-weighted MR images were obtained using the following parameters: repetition time (TR) = 550 ms; echo time (TE) = 10 ms; flip angle = 60°; field of view (FOV) = 21 cm; slice thickness = 3 mm; slice spacing = 0.1 mm. $H^1$-MRS was performed for quantification analysis of metabolite concentrations in the brain. Initially, 2D-T1W imaging data in the coronal and sagittal regions were obtained for image-guided localization of the voxels of interest for spectroscopic data acquisition. The MRS evaluation was conducted in the ACC and the basal ganglia (Fig. 1). Single-voxel MRS was performed using a stimulated-echo acquisition mode (STEAM) sequence with the following parameters: TR = 2000 ms; TE = 72 ms; mixing time (TM) = 6 ms; voxel = $20 \times 20 \times 20\ mm^3$; total number of points = 2048; averages = 256. Eight-step phase cycling was used to suppress unwanted signals or artifacts. The total scan time was 25 min. It was revealed that Glu was present at 2.35 ppm, Gln at 2.45 ppm, mI at 3.55 ppm, Cr at 3.02 ppm, and NAA at 2.01 ppm [12]. All these MRS metabolites were quantified by fitting experimental data in the frequency domain using the LC model algorithm.

### 2.5. Statistical analysis

Statistical analysis was performed using SPSS v.11.5 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as means (standard deviations), and categorical variables as frequencies or percentages. Differences between patients and healthy controls were tested using the two-tailed *t*-test. Differences within each group were tested with the paired *t*-test. The independent sample Student's *t*-test was used to compare metabolite concentration in the ACC and basal ganglia between the healthy controls