ORIGINAL ARTICLE

Correlation of Magnetic resonance brain imaging changes in chronic liver disease to manganese and ammonia levels

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Abstract

Background: Chronic liver disease patients may suffer from a wide spectrum of neuropsychiatric abnormalities that may be associated with cirrhosis and portal hypertension or portal-systemic shunts. Several neuroimaging techniques, especially MR imaging, could be useful for the diagnosis. Also, MRS can identify and measure various chemicals in the brain such as Choline (Cho), Myoinositol (MI), and glutamate-glutamine complex (Glx) that could be induced by liver injury.

Aims: To study the changes in MR brain imaging in CLD and their correlation to manganese and ammonia levels.

Methods: The study included 23 patients with CLD and ten healthy control subjects. MR brain was performed on all subjects including T1, T2, and FLAIR sequences, DWI and MRS. Grading of liver disease severity was done. Ammonia and manganese levels were measured in all patients.

Results:

Pallidal T1 Hyperintense signal was recognized in 15 patients. These signals correlated with the manganese levels (P=0.019). Hyperintense WMLs (white matter lesions) in FLAIR sequences were detected in 17 patients. MRS findings in patients with CLD included lower Cho/Cr and MI/Cr and higher Glx/Cr compared to controls (P < 0.05).

Conclusions: MRI and MRS can be used to detect metabolic brain abnormalities in CLD patients and quantify the degree of neurotoxicity. MRI and spectroscopy abnormalities are related to biological abnormalities (Ammonia and Manganese) associated with CLD.

Keywords: Chronic Liver disease (CLD), liver cirrhosis (LC), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), Ammonia (NH3), manganese (Mn)

INTRODUCTION

Manganese is an essential element that is normally excreted through the hepatobiliary route. Manganese (Mn) neurotoxicity was detected in patients with chronic liver disease because of the inability to excrete manganese via the biliary system. Manganese has been described to deposit in the basal ganglia appearing as hyperintense signals in T1 brain MRI [1, 2].

Hyperammonemia in patients with chronic liver failure can induce an increase in blood-brain barrier permeability, favoring capillary water influx to the brain leading to mild brain edema which can be detected by Fast FLAIR T2-weighted brain images [3].

Magnetic Resonance spectroscopy (MRS) provides information about the metabolic status of the tissues. MRS can provide information on brain metabolites such as Choline (Cho), Creatine (Cr), N-acetyl aspartate (NAA), Myo-inositol (MI), as well as glutamine and glutamate (Glx). Liver injury can alter the homeostasis of the principal metabolites in the brain [4].

Subjects and Methods

A written informed consent form was obtained from all study participants. A total of 23 adult patients with CLD (14 males and 9 females) with a mean age of 58 ± 8 years, in addition to 10 age and sex-matched healthy control subjects were recruited for this study.

All patients were subjected to history taking and clinical examination, routine labs, the severity of liver failure was graded using Child-Pugh's classification and MELD score.

MRI and MRS examinations were performed using a 1.5 Tesla MRI superconducting scanner (Intera; Philips Medical Systems Best, the Netherlands).

MRI examinations included:

- Axial T1WI to determine the signal intensity of the globus pallidus which was graded visually according to a 3-point grading scale (0 = no signals, +1= minimal, and +2= marked).
- Axial FLAIR to detect white matter changes.
- MR spectroscopy: MRS was performed using a single voxel technique at short TE and intermediate TE. Voxel was placed at the parieto-occipital white matter. Brain metabolites Cho, MI, and Glx were evaluated and compared at different time intervals to detect brain metabolite changes.

Fasting blood ammonia and serum manganese were measured on the same day of MRI examination and correlated with MRI findings.

For testing for Ammonia: One C.C blood sample was collected from each patient from a stasis-free vein. The samples were placed immediately on ice and centrifuged and sent to the lab as plasma EDTA Frozen. The analysis was performed within the same day of venipuncture. Sample analysis was performed with the enzymatic method using Cobas 6000 device. The reference range for males ranged from 16 to 60 umol/L and for females from 11 to 51 umol/L.

For testing for Manganese: Two C.C blood sample was collected from each patient. The samples were allowed to clot and centrifuged at room temperature. Serum was refrigerated at 2-8 o C. Sample analysis was performed ICP Mass Spectrometry (ICP-MS). The reference range was 0.5 - 1.3 ug/L.

Statistical methods:

All patient data were tabulated using Excel 2010. Data were processed using SPSS version 20 for Windows 2010. All qualitative data were analyzed using the chi-square test as appropriate. The chi-square test was used to calculate Pearson's chi-square and its P-value when both table variables were quantitative. Paired t-test or Wilcoxon rank tests were used to compare related samples according to normality tests. Differences for which $P > 0.05$ were not considered to be insignificant, differences for which $P < 0.05$ were statistically significant, and differences for which $P < 0.001$ were highly significant. The medical record profession has its code of ethics which applies to all medical record practitioners. Confidentiality of data, safe data storage, and privacy rights are respected by all who handle patient information. Data was coded and patient names or identities was not appearing in any of the data collection forms or during statistical analysis.

Results

Etiology and severity of liver disease:

Liver cirrhosis (LC) was due to HCV in 18 patients, HBV in 2, NASH in 2, and cryptogenic in 1.

The CHILD score ranged from 6 to 14 with a mean of 10.1 ± 2.6 while The MELD score ranged from 10 to 21 with a mean of 15.3 ± 3.6.

Ammonia and Manganese:

Ammonia levels in patients ranged from 54 to 95 with a mean of 75 ± 11.9 while Manganese levels ranged from 1.73 to 2.29 with a mean of 1.9 ± 0.19.

MRI:

Hyperintense T1 signals were detected in 15 patients (grade 1 in 6 patients and grade 2 in 9 patients) **(Figure 1)**
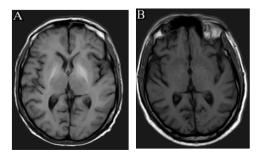

Figure. (1) Axial T1-WI MRI (A) CLD patient showing high signal intensity in globus pallidus (grade 2) and (B) Normal control showing no signal intensity.

WMLs in T2 FLAIR images were evident in 17 patients, these WMLs manifested as periventricular sheets (3 patients) or foci of WMLs (1 patient) or both (13 patients). **(Figure 2)**
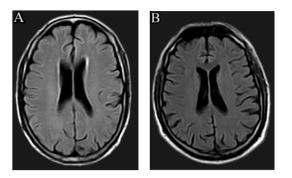

Figure. (2) Axial T2-weighted fast FLAIR images (A) in CLD patient showing peri-ventricular sheets of WMLs. (B) Normal control showing no WMLs.

MR brain imaging patients showed involutional brain changes in 11 patients (subjectively detected by the neuroradiologist).

Manganese levels were significantly positively correlated to the degree of hyperintense T1WI signals ($P = 0.019$).
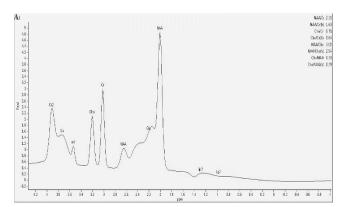
MRS

Comparing the metabolites Cho/Cr, MI/Cr, and Glx/Cr as measured by MRS in CLD patients with control group revealed that (**Table 1**)

Table (1) Comparing MRS findings in CLD and healthy control group:

	CLD	Control	P-Value
	Median	Median	
CHO	0.870	1.13	0.014
MI	0.348	0.98	0.001
GLX	0.735	0.53	0.02

CHO/Cr and MI/Cr were significantly lower in patients with CLD compared to normal controls ($P < 0.05$) while GLX/Cr is significantly higher ($P < 0.05$). **(Figure 3)**

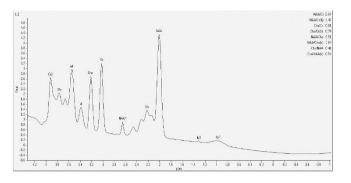Correlation between Ammonia, Manganese, MRS, and T1WI:

Figure. (3) MRS (A) CLD patient showing low Cho/Cr and MI/Cr peaks and high Glx/Cr peak (B) Normal control showing high Cho/Cr and MI/Cr peaks and low Glx/Cr peak

The Ammonia levels were significantly negatively correlated with MI/Cr ($P = 0.028$) while the Manganese levels were significantly positively correlated with Glx/Cr ($P = 0.03$).

Both Cho/Cr and MI/Cr levels were negatively correlated to the T1 hyperintense signals ($P = 0.038$ and 0.004 respectively).

Discussion

The current study aims to detect changes in MR brain imaging abnormalities in patients with CLD and to correlate them to the serum levels of manganese and ammonia.

The fact that most patients with cirrhosis or portosystemic shunts show a bilateral symmetric high signal intensity at the basal ganglia has been described [2].

The most accepted explanation for the basal ganglia hyperintensities is the presence of manganese (Mn) at high concentrations where an inability to excrete manganese via the biliary system causes increased serum levels. Mn has been found to deposit in the basal ganglia [5].

In our study, fifteen out of 23 cirrhotic patients showed bilateral pallidal hyperintense T1 signal (six patients grade 1 and nine patients grade 2). Manganese levels were elevated in all patients with decompensated CLD. We have found a significant positive correlation between the degree of hyperintense signal in T1WI and blood manganese levels in CLD patients ($P = 0.019$).

MRI brain T2 signal hyperintensity was detected along with the hemispheric white matter in or around the corticospinal tract in cirrhotic patients in few previous studies. This may be due to is the presence of mild brain edema likely related to hyperammonemia [6].

In the present study, white matter lesions (WMLs) have been noted in T2 FALIR WI in 17 patients. These WMLs have manifested as periventricular sheets (3 patients) or foci of WMLs (1 patient) or both (13 patients). Ammonia levels in our study were elevated in 19 patients.

MRS can identify and measure various chemicals in the brain. Liver injury can change the brain metabolites, Choline (Cho), Myoinositol (MI), and glutamate-glutamine complex (Glx). Choline (Cho) is the precursor of acetylcholine and is known to be associated with memory and cognitive activity and myelin sheath integrity. Myoinositol (MI) maintains osmotic pressure and membrane integrity. Glutamate, the primary CNS excitatory neurotransmitter, and glutamine, an amino acid

metabolically coupled to glutamate are together termed the glutamate-glutamine complex or Glx [4].

In the current study, all CLD patients have shown a high Glx/Cr ratio together with a low Cho/Cr ratio and a low MI/Cr ratio compared to healthy controls ($P < 0.05$). This was similar to the findings of some previous studies which reported a decrease in MI/Cr and Cho/Cr ratios accompanied by an increase in Glx/Cr ratio in CLD patients [7].

Additionally, we have found a negative correlation between T1WI hyperintense signal and Cho/Cr and MI/Cr levels ($P < 0.05$) in CLD patients. These findings are in opposition to the findings by Tarasow et al; 2003 who didn't observe any significant correlations between hyperintensities in globus pallidus and metabolite ratios in 34 patients with CLD [8].

We have also found a negative correlation between Ammonia levels and MI/Cr ratio ($P = 0.028$) as well as a positive correlation between Manganese levels and Glx/Cr ratio ($P = 0.03$). These findings were in partial agreement with the study conducted by Long et al; 2009 on 50 cirrhotic patients and revealed that blood ammonia levels positively correlated with Glx/Cr ratio. However, Manganese levels did not correlate to any other MRS parameters in their study [9]. In addition, Zhang et al; 2010 found that venous ammonia had a significant negative correlation with Cho/Cr and MI/Cr in 52 cirrhotic patients [10].

Eleven patients in our study have shown involutional brain changes. In agreement with our findings, Guevara et al; 2011 performed a study on 48 cirrhotic patients to assess brain tissue density and found decreased density in several gray and white matter areas that progressed during the disease [11].

Conclusion

MRI and MRS could be used to assess the morphological and metabolic abnormalities in the brain in patients with CLD and quantify the degree of neurotoxicity. In addition, estimation of serum ammonia and manganese could be useful in the evaluation of patients with CLD as they correlate to metabolic brain abnormalities.

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