Assessment the Role of L-Carnitine in Improving Hepatic Encephalopathy Using MR Spectroscopy

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Abstract: Background and aim: Hepatic encephalopathy (HE) is related to abnormal cerebral metabolites. MR Spectroscopy (MRS) can demonstrate neurometabolites changes associated with therapy. The aim was to evaluate the influence of L-carnitine on mental Conditions, serum ammonia and neurometabolites on patients with HE using MRS. Patients and methods: Ten control subjects and 54 patients with grades II to III HE, were randomized into (GI) receiving lactulose 30ml/t.d.s as standard therapy and(GII) receiving L-Carnitine1000mg/twice in addition. Clinical assessment, fasting Ammonia level, and nuerometabolites using proton MRS were calculated and compared at base line and after one week. RESULTS: After one week, 25% of HE patients were reversed in group I versus 42.3% in group II. fasting ammonia levels were significantly decreased in both groups compared to pretreatment levels and significantly lower in L-carnitine group compared to lactulose group(P=0.041). neurometabolites mI/Cre, Cho/Cre, Gx/Cre, and (Cho+mI)/Gx ratios were significantly improved in both groups compared to pre treatment levels, but L Carnitine added group(II), showed a significant increase in mI/Cre, and (Cho+mI)/Glx ratios and decrease in Glx/Cre ratio in comparison to lactulose group(p=0.002-p=0.003-p=0.002 respectively). CONCLUSION: Adding L Carnitine to (lactulose) therapy for treatment HE hastened the clinical improvement and was associated with significant improvement in serum ammonia and neurometabolites specially mI/Cre, and (Cho+ mI)/Glx and Glx/Cre ratios .

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Key words: Magnetic Resonance Spectroscopy (MRS), L-Carnitine, hepatic encephalopathy (HE), neurometabolite.

1. Introduction

Hepatic encephalopathy comprises a spectrum of neuropsychiatric abnormalities that range from clinically indiscernible changes in cognition, obvious changes in intellect, behavior, motor function, and consciousness up to coma[(1)] .

The pathogenesis of HE is multi factorial, Disturbances in neurotransmitter balance, cerebral metabolism, blood-brain barrier integrity, and sodium-potassium–adenosine triphosphatase activity have been implicated [(2-5)].

Although the exact neurotoxins involved remain poorly defined, ammonia is thought to play a central role in all hypothesis[(6-8)]. In hyperamoniamea state astrocytes protect the brain by converting ammonia into glutamine as it contains glutamine synthtase. Glutamine is not toxic, but it is osmotically active, and as it accumulates, it leads to astrocyte swelling and brain edema. Besides, astrocytes are responsible for integrity of blood brain barrier, so their swelling facilitate further ammonia accumulation in the brain[(9)].

Carnitine and its esters are naturally present in meat and dairy products. It is a conditionally essential nutrient that plays a vital role in energy production and involved in regulating cell membrane permeability and intracellular energy. Levo carnitine participates in the control of peroxisomal oxidation of fatty acids and mitochondrial acyl-CoA/CoA ratio to prevent adenylate translocase inhibition of the activity of pyruvate dehydrogenase and thus enhancing the oxidative utilization of glucose[(10)].

Carnitine as a nutritional supplement has been promoted as beneficial in a number of disorders of human since the 1960s. It has been reported to have a protective effect against ammonia-precipitated encephalopathy in cirrhotic patients and in valproic acid induced hyperammonemia[(11-12)]. Its use was associated with significant reduction of blood and brain ammonia concentration in many studies in mice, rats, and human beings[(10-11,13-14)]. In our previous experimental study we demonstrate that L - Carnitine can affect not only brain ammonia but also some other metabolites like tryptophan and seretonine[(14)] .

Proton MR spectroscopy is non invasive modality that use MRI to study specific tissue metabolites. In hepatic encephalopathy, many studies have demonstrated its ability to detect and measure metabolic abnormalities in brain, including reduced myo-inositol (mI) and Choline (Cho), and increased glutamine . It can also detect neurometabolic changes

associated with HE pre and post pharmacologic therapy[15]. However, MR spectroscopy is not widely used to assess HE, which is still diagnosed by using clinical categorical scales[16-19].

This work used MRS as precise tool to evaluate the brain metabolic changes associated with administration of L-Carnitine in hepatic encephalopathy patients.

3. Patients and Methods

This study was performed on 64 cases. Fifty four patients were diagnosed as grad II or III hepatic encephalopathy using the criteria of Parsons-Smith *et al.,* 1957[20], admitted to Tropical Medicine and Infectious Disease and Internal Medicine Departments, Tanta University hospitals in period between March 2010 and August 2011 were randomly assigned into two matched groups GI: 28 patient received standard therapy in the form of oral lactulose and frequents enemas , and GII: 26 patients received L carnitine capsule 1000 mg twice/day in addition to same standard therapy received in group I. Ten age and sex matched cases with healthy liver, referred to Diagnostic Radiology Department for brain MRI examination, who had normal brain MRS examination as a control group.

This study is a controlled clinical trial. A placebo-controlled trial without lactulose was considered unethical in this study, since lactulose has already been approved as effective therapy in HE.

This protocol was approved by the institutional human research ethical committee (IHREC). Informed consent was obtained from patient's guardians- as patient's mental state doesn't allow for legal consents- before they participated in the study. Patients were compared to before and after therapy, to detect the therapy response regardless innate variables, including degree of disease severity, genetic factors, and individual habits, including diet. Both groups were compared before therapy for matching and after therapy for difference. To assure that spontaneous changes unrelated to therapy were minimized, we kept all patients on a stable protein-restricted diet before and during the study.

At base line, patients with hepatic encephalopathy were clinically assessed; fasting ammonia level and MRI with MR spectroscopy were performed. Regardless the results, they were randomized into either group I or II

Group (I) received lactulose 30 ml three times per day

Group (II) received the same therapy in addition to L-carnitine capsule 1000mg twice/day, the patients were clinically assessed daily and restudied for fasting ammonia level and MRS on day 8. The responses of HE grade and neurometabolites to both therapies were reported and compared.

MRI examination of brain:

All patients were evaluated by MRI technique using 1.5 Tesla superconducting MR imager, in a supine position with a standard circularly polarized head coil. Axial T1 WI [400 /14 ms (TR/TE)] spine Cho, T2 WI (4000/127 ms) turbo spine Cho and fast liquid attenuation inversion recovery (FLAIR) [9000/127/2800 ms (TR/TE/TI)] were obtained by using 5 mm section thickness.

During MRS examination; to allow for precise measuring of brain metabolites, multiple voxels were positioned at both basal ganglia using point resolved spectroscopy (PRESS) with parameters TR/TE 1000/144 and 1500/35. Both long and short TE (144 & 35 ms) respectively were used, long TE was used to clearly visualize peak intensity of Choline(Cho) , creatine(Cre) , N-acetylaspartate(NAA) , glutamin ,glutamate(Glx), and myo-inositol(mI); to obtain Cho/Cre mI/Cre, Choline, (glutamine+ glutamate)(Glx)/Cre, NAA/Cre, and (Cho+mI)/Glx ratios, and to determine the presence of Lac, while short TE was mainly used just to illustrate Lip peak.Frequency domain curve was fitted to Gaussian line shape by using the software provided by the manufacturer to define NAA at 2.02 ppm, Cho at 3.22 ppm, Cr at 3.01ppm, Lip at 0.9 and 1.33 ppm, and Lac at 1.33 ppm metabolic values were calculated automatically from area under each metabolic peak using the standard software program provided by the manufacturer and and from these metabolic values the different ratios were obtained.

Statistical analysis:

Statistical analyses were conducted using SPSS ver. 13. Categorical data were analyzed using Chi square . Means of groups were compared with the two-tailed t-test. Paired data obtained before and after therapies were compared with the paired difference t-test. For all used tests 95% confidence interval was adopted and $p<0.05$ considered significant.

3. Results:

Out of 64 cases included in this study, Ten subjects (7 males, 3females) had normal liver functions serve as control group, 54 cirrhotic patients with hepatic encephalopathy were randomized prospectively in two groups who were matched as regard age and sex, There was no significant demographic difference between the two groups at base line (Table 1).

Clinically, 23/28 of group I had grad III encephalopathy compared to 22/26 in group II. First case clinically improved to grade (0) occurred by day

4 in group (I) compared to day 2 in group II. By day 8, 7/28 (25%) of HE patients were reversed in group I versus 11/26 (42.3%) in group II ((p= 0.017*) (Table 2).

Table (1) Demographic data of all studied patients

	Control group (n=10)	Lactulose group (GI) (n=28)	L Carnitine group(GII) (n=26)
Male/female	7/3	20/8	18/8
age	57.7±4.64	55.14±6.72	57.29±7.7
Child class A	10	0	0
B	0	9	8
C	0	19	18
INR	0.99±0.07	2.06±0.36	1.96±0.34
Albumin(g/dL)	4.27±0.26	2.78±0.28	2.77±0.31
ALT (IU/L)	30.6±5.44	58.46±18.67	50.73±16.73
AST(IU/L)	29.1±4.04	62.54±23.64	66.35±32.85
Bilirubin (mg/dL)	0.75±0.16	2.99±1.30	3.26±1.66
Child score	4.4±0.52	10.75±1.67	10.69±1.72
Serum Creatinine (mg/dL)	0.83±0.16	1.6±0.40	1.4±0.27
Fasting serum Ammonia level	40.1±25.1	87.1±35.2	89.2±34.2

Table (2): Clinical follow up of both hepatic encephalopathy groups

	Lactulose group (I) (n=28)				L- Carnitine group (II) (n=26)			
days	Grade III	Grade II	Grade I	Grade0	Grade III	Grade II	Grade I	Grade0
1	23	5	0	0	22	4	0	0
2	20	7	1	0	19	4	3	0
3	15	9	4	0	11	8	5	2
4	12	10	5	1	8	9	7	2
5	10	8	8	2	7	8	6	5
6	7	11	6	4	3	8	8	7
7	4	10	8	6	1	7	8	9
8	1	12	8	7	0	6	9	11
X^2	5.746 (p= 0.017*)							

Fasting ammonia levels were significantly higher in both groups in comparison with control group. By day 8, post treatment fasting ammonia levels were significantly decreased in both groups compared to pretreatment levels (p<0.001-p<0.001). Comparing lactulose group and L-carnitine post-treatment, NH4 level was significantly lower in L-carnitine group (p=0.041).

T1 weighted MRI examination showed slight cerebral edema and hyperintensity of basal ganglia in hepatic encephalopathy patients compared with control group (Fig 1). Neurometabolites were studied using MRS in all studied groups at base line, mI/Cre, Cho/Cre, and (Cho+mI)/Glx ratios were significantly lower in patients with hepatic encephalopathy compared to control group while Glx/Cre, ratio was significantly higher. There was no significant difference in these ratios between both encephalopathy groups at base line (Table 3-Figs. 2A-3A).

Table (3): Neuro-metabolites ratios in all studied groups at base line using MRS.

Metabolite (mean ± SD)	Control group (n=10)	Lactulose group (GI) (n=28)	L- Carnitine group (GII) (n=26)	p_1	p_2	p_3
mI/Cre	0.9 61± 0.36	0.314 ±0.154	0.250±0.186	<0.001*	<0.001*	0.173
Cho/Cre	0.40 6±0.05	0.281± 0.071	0.266±0. 039	<0.001*	<0.001*	0.34
Glx/Cre	2.26 6±0.14	4.00 6± 0.96	3.835±0.887	<0.001*	<0.001*	0.491
NAA/Cre	1.829 ± 0.172	1.919±0.123	1.870±0.076	0.081	0.323	0.081
(Cho+mI)/Glx	0.84 ±0.21	0.37 6± 0.16	0.391± 0.09	<0.001*	<0.001*	0.676

$p_{1=}$ difference between control and lactulose groups
$p_{2=}$ difference between control and L Carnitine groups
$p_{3=}$ difference between lactulose and L Carnitine groups
*= p<0.05 (significant)

Table (4): Fasting ammonia levels and neuro-metabolites ratios in patients with hepatic encephalopathy before and after therapy.

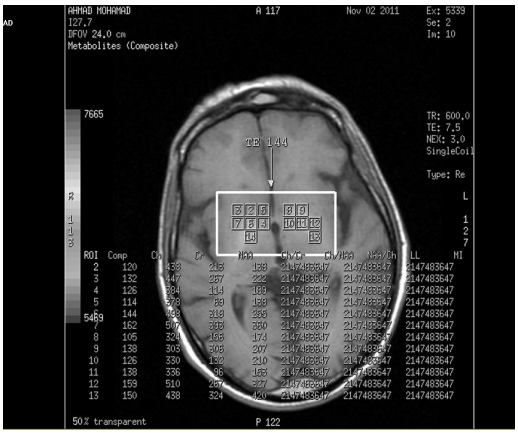
Metabolite (mean ± SD	Lactulose group (n=28)			L- Carnitine group (n=26)		
	Before	After	p	Before	After	p
Fasting NH4 µmol/L	87.1±35.2	59.2±19.8	<0.001*	89.2±34.2	45.4±28.1	<0.001*
mI/Cre	0.314± 0.154	0.62 6± 0.28	<0.001*	0.250±0.186	0.821±0.132	<0.001*
Cho/Cre	0.281± 0.071	0.366±0.16	0.013*	0.266±0. 039	0.391±0.04	<0.001*
Gx/Cre	4.00 6± 0.62	2.992±0.62	<0.001*	3.835±0.887	2.458±0.590	<0.001*
NAA/Cre	1.919±0.123	1.844±0.257	0.187	1.870±0.076	1.801±0.305	0.268
(Cho+mI)/Gx	0.37 6± 0.16	0.489± 0.23	0.037*	0.391± 0.09	0.631±0.012	<0.001*

Table (5): Comparison between fasting ammonia levels and neurometabolite ratios in both studied groups post treatment.

Metabolite ratio (mean ± SD)	Post Lactulose therapy (n=28)	Post L Carnitine therapy (n=26)	p
Fasting NH4 µmol/L	59.2±19.8	45.4±28.1	0.041*
mI/Cre	0.626± 0.28	0.821±0.132	0.002*
Cho/Cre	0.366±0.16	0.391±0.04	0.442
Glx/Cre	2.992±0.62	2.458±0.590	0.002*
NAA/Cre	1.781±0.257	1.760 ±0.305	0.785
(Cho+mI)/Glx	0.489± 0.23	0.631± 0.012	0.003*

One week after therapy, neurometabolites mI/Cre, Cho/Cre, Gx/Cre, and (Cho+mI)/Gx ratios were significantly improved in lactulose and L-carnitine groups compared to pre treatment levels (Table 4-Figs. 2B-3B).

Comparing both groups to each other, post lactulose therapy alone group(I)to L Carnitine added group(II), mI/Cre, and (Cho+mI)/Glx ratios were significantly increased and Glx/Cre ratio was significantly decreased in group (II) in comparison to Post lactulose group(p=0.002-p=0.003-p=0.002 respectively). While Cho/Cre and NAA/Cre ratios were not significantly different in both groups (Table 5).



Fig(I): Axial T1 W image shows slight cerebral edema and hyperintensity of basal ganglia and multivoxal box for MRS.

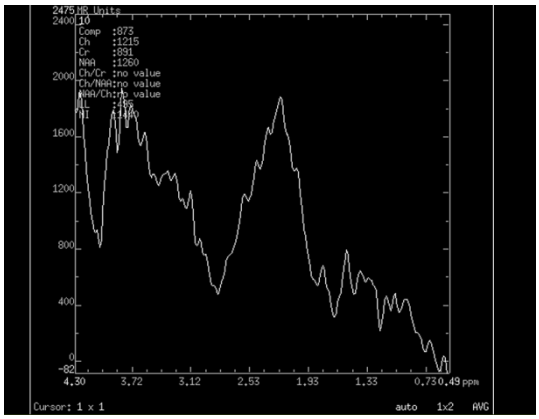


Fig. 2A

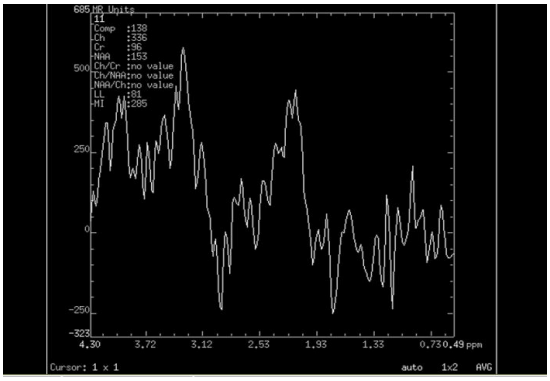
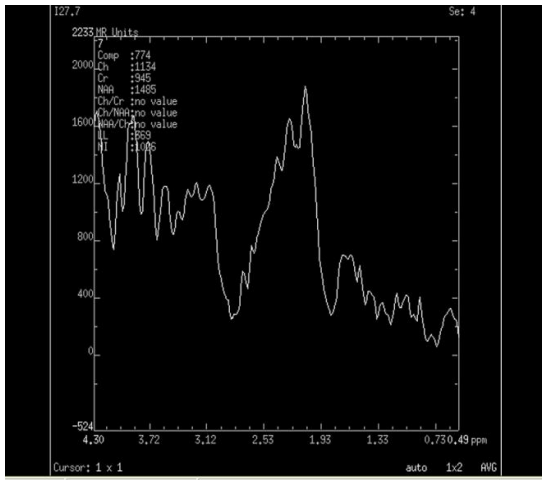
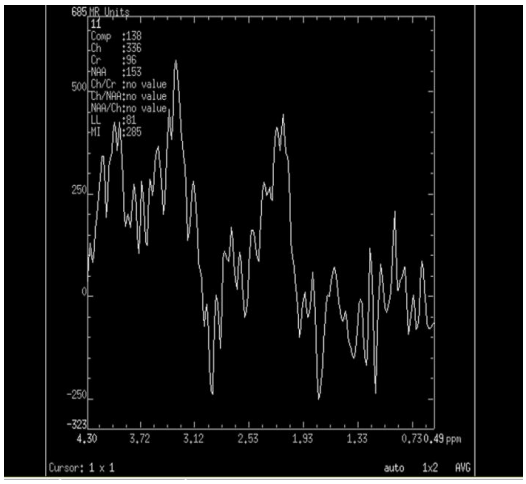


Fig. 2B

Fig(2) Pre – therapy in a 45 years old patient with hepatic encephalopathy reveals high Glx, and noticeable decrease in choline Proton MRS(Fig2A)after therapy shows definite reduction in Glx , and increased in choline and increased MI(Fig2B) -





Fig(3A) **Fig(3B)**

Figure 3: Pre – therapy in a 55 years old patient with hepatic encephalopathy reveals high Glx, and noticeable decrease in choline (Fig3A)- Proton MRS after therapy shows definite reduction in Glx , and increased in choline and increased MI (Fig 3B) -

4. Discussion:

The pathogenesis of hepatic encephalopathy is multi factorial, Gut-derived nitrogenous substances are thought to play a central role in all hypothesis .Despite its key role, an ammonia level is merely a data point among the constellation of variables that may contribute to the development of HE and, for now, the final diagnosis remains a clinical one.

Both venous and arterial ammonia levels were poorly correlated to brain ammonia and grade of HE(21) . Which explain our data as patients with HE on therapy showed clinical improvement by at least one grade in most of the cases. This was associated with significant reduction of mean ammonia level ,but reduction of ammonia in each patient was not correlated to degree of clinical improvement .

Formerly, the studying of brain neurometabolite was problematic. *In vivo* studies were performed only in animals. Now, MRI examination and 1H magnetic resonance spectroscopy (MRS) enables the noninvasive recording of these metabolites *in vivo* in human(16-17).

In our patients with hepatic encephalopathy, the T1 weighted MRI examination shows slight cerebral edema and hyperintensity of basal ganglia compared with control group. This agree with data previously reported in patients with cirrhosis where metabolic disturbances are associated with increased brain water, and its severity correlates with worsening of neuropsychological function (22-27) . Globus pallidal (GP) hyperintensities in T1-weighted MRI examination of cirrhotic patients and portal encephalopathy was also reported (27-28).

In hepatic encephalopathy, decreased urea cycle activity due to liver dysfunction could lead to astrocyte swelling which induces high intracellular glutamine concentrations, and mI release was suggested to be a cellular compensatory mechanism and suggested to be a major cause of the development of HE(25) These findings are partly based on the studies in which hyperammonemia directly influence the astrocyte swelling in patients with valproate medication or toxicity(29) and elevated cerebral glutamine level owing to its increased synthesis in astrocytes (25). However, the exact roles of Cho and mI in the brain, and especially in HE, are not completely understood. Levels of mI and Cho in HE may be reduced due to osmotic mechanisms associated with glutamine accumulation, decreased hepatic synthesis, decreased dietary intake, or increased consumption of metabolites in an attempt to compensate for hepatic failure (25). In addition, mI contributes to ion flux, and may serve as an organic osmolite which play an important role in the volume regulation of astrocytes (30-31). That can explain the substantial changes in cerebral mI/Cr and Cho/Cr ratios, with or without a Glx/Cr ratio change, which was described exclusively in hepatic encephalopathy rather than other encephalopathies (32).

These findings were confirmed in our patients where there was a significant increase in the levels of glutamate plus glutamine (Glx), and significant decreases in Cho and mI with subsequent significant lower mI/Cre, Cho/Cre, and (Cho+mI)/Glx ratios and significantly higher Glx/Cre ratio in patients suffering

hepatic encephalopathy compared to control, while NAA/Cre ratio was non significantly different in encephalopathy patients when compared to control. **Naegele *et al.,* 2000**(33) reported normalization of Cho, and MI to occur 5-7 months after orthotropic liver transplantation with restoration of normal MR spectroscopic profile one year After successful transplantation. Our patients with hepatic encephalopathy showed significant improvement in their consciousness level as well as their neurometabolic ratios mI/Cre, Cho/Cre and (Cho+ mI)/Glx but not NAA/Cre in both groups, but they don't reach normalization in their brain metabolites. This was in accordance with **Ross *et al.,* 1996**(34) who reported conventional drug therapy to improve both clinical picture of HE and MR spectroscopic profile but not to restore the normal MR spectroscopic profile.

The beneficial effects of oral lactulose on HE was proven long time ago. This effect may be attributable to reduction in gut transit time, reduction in ammonia absorption by conversion of ammonia to the poorly absorbable ammonium ion and decrease in ammonia production in situ by bacteria(35-37). So, it was expected for patients receiving lactulose to be improved. However, adding L Carnitine significantly hasten the clinical improvement to reach 42.3% reversal of HE versus 25% for patients on lactulose only. This effect can be attributed to ammonia reduction as it was reduced more significantly in patients received L Carnitine than those on lactulose only. As oral administration of L-Carnitine for 4 wks corrects hyperammonemia in patients treated with valproic acid(12,38). Ammonia reduction and psychometric test improvement were previously reported in cirrhotic patients received L-carnitine(11,39).

In our patients, it was not only about reduction of ammonia but neurometabolites also were significantly more improved regarding mI/Cre, Glx/Cre, and (Cho+mI)/Glx ratios in patients received L Carnitine compared to lactulose alone. This may be explained by its biochemical effects. As L-carnitine administration has been reported to accompany with a significant attenuation of the increased cerebrospinal fluid and brain alanine as well as cerebrospinal fluid lactate content, suggesting that mitochondrial respiration is at least partially restored in L-carnitine-treated animals. This beneficial effect may be related to an improved pyruvate oxidation, Krebs cycle and flux through glutamate dehydrogenase. The latter which could explain the lowering of blood ammonia levels that follows L-carnitine administration(40) . In addition to the repotted studies which demonstrate that L - Carnitine can affect some other metabolites like tryptophan and seretonine(14) .

There was no adverse effects could be attributed to the use of L Carnitine therapy in our patients. This was in agreement with **Malaguarnera *et al.,* 2005**(39) who reported L Carnitine therapy to be effective with minimal adverse events when used in cirrhotic patients with hyperammonemia .

Conclusion:

Adding L Carnitine to conventional therapy (lactulose) for HE hastened the clinical improvement and was associated with significant improvement in serum ammonia and neurometabolites ratios.

MRS is useful tool for precise measurement of neurometabolites and its changes in response to therapy and a helping device to understand the pathophyiology of HE.

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