Research Paper

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Neurometabolites Alterations Judged by Magnetic Resonance Spectroscopy may Underlie Chronic Hepatitis C associated Fatigue

Medical Science

KEYWORDS : Chronic Hepatitis C, Fatigue, Neurochemicals, MR spectroscopy

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ABSTRACT

Objectives: To evaluate the relationship between chronic hepatitis C (CHC) and severity of fatigue and to determine neurochemicals alterations using magnetic resonance spectroscopy (MRS) Patients & Methods: 100 CHC were categorized using modified Child-Pugh classification and underwent evaluation of quality of life using CLDQ questionnaire, sense of fatigue using FSS, global fatigue using the 11-point visual analogue fatigue scale (VAFS) and to determine the impact of fatigue on their daily life using MFIS. All patients underwent MRI and MRS examinations. Results: Mean total CLDQ score and VAFS mean score as well frequency of lower MFIS of Class A patients was significantly higher than Class B and C and in Class B than Class C. Mean FSS of Class A patients was significantly lower compared to other patients. Mean total MFIS score was significantly lower in Class A than in Class C patients. Neurochemicals concentration was significantly decreased in all patients than controls with significantly lower NAA concentration in Class C than in Class A patients. Conclusion: Fatigue is a prominent complaint of CHC patients and is magnified with the more liver derangement and mostly associated with altered concentrations of neurochemicals judged by MRS.

Introduction

Fatigue sensation plays an important role as a biological alarm under the conditions of fatigue and urges subjects to take a rest to avoid upsetting homeostasis and to recover from fatigue. In this sense, the fatigue sensation is beneficial for survival. However, over-activation of the fatigue sensation might be involved in the pathophysiology of fatigue-related diseases [1, 2]. On the other hand, fatigue is one of the most common complaints of patients with chronic diseases, but despite its significance as a crucial issue for health care, its evaluation was hampered by its highly non-specific nature [3, 4].

Chronic hepatitis C (CHC) virus infection is known to be associated with impaired health related quality of life and patients always have higher rates of psychiatric disorders than the general population. Depressive disorders were associated with worse scores in overall health related quality of life and in all domains. Fatigue was associated with lower scores in physical and psychological domains, and married status with higher scores in psychological health related quality of life. There is strong correlation among scores of depression, fatigue and health related quality of life of CHC patients [5, 6].

Multiple studies tried to explore the underlying mechanisms for development of fatigue in association with CHC infection; Pavić et al. [7] reported that the presence of depression was more often in patients with CHC viral infection compared to healthy population and the presence of depression caused deterioration of the physical and mental components of the quality of life manifested as fatigue, loss of self-confidence, reduced working capacity, development of emotional problems, and cognitive dysfunction. Anty et al. [8] found that patients with CHC had significant lower plasma levels of total and free carnitine adjusted for fat mass compared with healthy subjects, fatigue scores were negatively correlated with plasma levels of carnitine and levels of free carnitine were significantly and independently associated with the severity of fatigue in CHC patients. El-Gindy et al. [9] found serum leptin level was significantly higher in CHC patients compared to control subjects and it was not related to severity of liver disease, but was directly correlated to the severity of fatigue in patients but not in the control subjects and concluded that increased serum leptin levels may underlie the development of fatigue.

The current study aimed to explore the relationship between severity of CHC disease and occurrence and severity of fatigue and to determine the alterations of neurometabolites as judged by magnetic resonance spectroscopy (MRS) and its relation to modified fatigue impact scale (FIS) scores

Patients & Methods

The current prospective comparative study was conducted at King Fahd Hospital, and Saudi_German Hospital, Madinah, KSA since March 2011 till Oct. 2013. After approval of the study protocol by the Local Ethical Committee and obtaining written fully informed patients' consents, 100 CHC patients were enrolled in the study. Patients had hepatitis for other causes than hepatitis C infection were excluded from the study.

All patients underwent determination of demographic data including age, gender, smoking, degree of education and occupation. Then, patients were categorized according to severity of liver disease using modified Child-Pugh classification of severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease; 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease) as shown in table 1[10].

Table (1) Child-Pugh Classification of Severity of Liver Disease [10]

Parameter		Points assigned		
		1	2	3
Ascites		Absent	Slight	Moderate
Bilirubin (mg/dl)		≤2	2-3	>3
Albumin (g/dl)		>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds over control	1-3	4-6	>6
	INR	<1.8	1.8-2.3	>2.3
Encephalopathy		None	Grade 1-2	Grade 3-4

Then, all patients underwent evaluation quality of life using the chronic liver disease questionnaire (CLDQ). The CLDQ is the first liver specific instrument developed by Younossi et al.

[11] and includes 29 items in the following domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry. The response of CLDQ results in 1 to 7 scales: ranging from "all of the time" to "none of the time" with higher scores indicating low impact of CLD and lower score indicated high impact. The validity of original CLDQ was approved by multiple studies in chronic liver diseases [12, 13].

Instruments for assessment of fatigue and its impact on quality of life

1. All patients underwent evaluation of their sense of fatigue using the Fatigue Severity Scale (FSS); each patient was asked to circle the number between 1 and 7 which he/she feels best fits the nine statements concerning his/her sense of fatigue during the usual way of life within the last week, where 1 indicates "strongly disagree" and 7 indicates "strongly agree.", (Table 2) [14].
2. Then, patients were asked to determine their global fatigue using the 11-point visual analogue fatigue scale (VAFS) with 0 being worst and 10 being normal.
3. Finally, patients were asked to determine the impact of fatigue on their daily life using Modified Fatigue Impact Scale (MFIS). The MFIS (Fig. 1) is a modified form of the Fatigue Impact Scale [15] based on items concerning how fatigue impacts patients' lives. This multidimensional instrument includes physical, cognitive, and psychosocial subscales and assesses the impact of fatigue on a variety of daily activities. The MFIS consists of 21 items each item is scores from 0 to 4 with 0 indicated no impact and being normal, while 4 indicated worst impact [14, 16].

Table (2): Statements and scores of Fatigue Severity Scale

Statements	Scores						
	1	2	3	4	5	6	7
1. My motivation is lower when I am fatigued							
2. Exercise brings on my fatigue							
3. I am easily fatigued							
4. Fatigue interferes with my physical functioning							
5. Fatigue causes frequent problems for me							
6. My fatigue prevents sustained physical functioning							
7. Fatigue interferes with carrying out certain duties and responsibilities							
8. Fatigue is among my most disabling symptoms							
9. Fatigue interferes with my work, family, or social life							



Fig. (1): The 21-item Modified Fatigue Impact Scale [16]

MR Spectroscopy

All the MRI and MRS examinations were performed on a 3.0 T MR scanner (Philips Achieva, Netherlands). The traditional MR imaging sequences included fast spin-echo T2-weighted images (TR/TE 4000/100 ms) and spin-echo T1-weighted images (TR/TE 500/15 ms) in three orthogonal planes. Single-voxel MR spectroscopy was performed using stimulated echo acquisition mode (STEAM) sequence. Both unsuppressed tissue water and metabolite with water suppression spectra were acquired, with the following parameters: TR/TE/TM = 2000/20/16 ms, spectral bandwidth =2000 Hz, data points = 1024, number of signals averaged = 128 for metabolites and tissue water, and scanning time = 4 minutes and 56 seconds. VOI was placed in the left DLPFC, ACC, the left and right putamens and the left thalamus. The Mean6SD VOI volume was 3.560.2, 3.460.3, 2.860.2, 2.960.2, 3.260.3 cubic centimeters, respectively. Shimming, frequency adjustment, and water suppression were automatically accomplished before data acquisition. Raw spectral data were exported and processed using jMRUI 3.0. Phase correction and 3 Hz Lorentzian apodization were first performed, and then tissue water and metabolite (including NAA, Cr and Cho) peak areas were obtained using 'Advanced Method for Accurate, Robust and Efficient Spectral fitting (AMARES)' package. Prior knowledge including chemical shift (NAA at 2.02 ppm, Cr at 3.03 ppm and Cho at 3.22 ppm with a deviation range of 60.05 ppm for all), lineshape (Gaussian lineshape was used for all), line width (the initial value set for simulation was 4 Hz and was allowed to vary within a range of 1–8 Hz) was incorporated into the fitting algorithm. Soft constraints were applied to all the simulations. And then, absolute metabolite concentration was calculated using tissue water as the internal reference [17, 18, 19]. Tissue water concentration used was 35 mol/kg wet weight [20, 21, 22] and the

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T1 and T2 relaxation constants of tissue water and metabolites were obtained from reported values under the same field strength and the same sequence (STEAM) [23, 24, 25]. To correct the partial volume effect of cerebrospinal fluid (CSF) contained in the VOIs of ACC and left DLPFC, segmentation of the T2-weighted images was performed as we previously described [26]. The volume of CSF in each slice was calculated by multiplying their areas with slice thickness, and their summation gave total volume of CSF parts within the voxel. We assumed that CSF parts contributed to tissue water rather than to metabolite, and the corrected metabolite concentration was calculated as follows: Corrected metabolite concentration = metabolite concentration 6VOI volume/ (VOI volume 2 CSF volume).

Results

The study included 100 chronic hepatitis C patients; 56 males and 44 females with mean age of 53.8±8.4; range: 41-69 years. Twenty-six patients were current smokers and 13 patients were ex-smokers. Only 31 patients were college graduate, 41 patients were secondary and high school graduate, 15 patients were primary school graduate and 13 patients were illiterate. Twenty-four patients were employee, 15 patients were retired and 61 patients were unemployed. Sixty patients were married, 13 patients were divorced and 18 patients were widows, while 9 patients were still single. The underlying etiology for chronic liver disease was viral infection; patients with other etiologies were excluded from the study. According to Child-Pugh grading of cirrhosis; 45 patients were of CP class A, 36 patients were of class B and 19 patients were of class C, (Table 3).

Table (3): Patients' demographic and clinical enrolment data

Data				Findings
Age (years)	Strata	40-50	Number	40 (40%)
			Mean	44.8±2.1 (41-49)
		>50-60	Number	36 (36%)
			Mean	56.1±1.9 (51-59)
		>60	Number	24 (24%)
			Mean	65.3±1.9 (62-69)
	Total			53.8±8.4 (41-69)
Gender	Males			56 (56%)
	Females			44 (44%)
Smoking	Current smokers			26 (26%)
	Ex-smokers			13 (13%)
	Non-smokers			61 (61%)
Education	Illiterate			13 (13%)
	Primary school			15 (15%)
	Secondary school			18 (18%)
	High school			23 (23%)
	University			31 (31%)
Current employment status	Employed			24 (24%)
	Unemployed	Manual workers		19 (19%)
		Farmers		20 (20%)
		Housewives		22 (22%)
	Retired			15 (15%)
Marital status	Single			9 (9%)
	Married			60 (60%)
	Divorced			13 (13%)
	Widowed			18 (18%)
Child-Pugh class	Child's A			45 (45%)
	Child's B			36 (37%)
	Child's C			19 (19%)

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis

Mean total CLDQ score of Class A patients was significantly ($p<0.05$) higher compared to that of patients of Class B and C patients with significantly ($p<0.05$) higher mean total CLDQ score recorded in Class B patients compared to those of Class C, (Fig. 2). As regards the individual domains; mean total scores of abdominal symptoms and emotional function were significantly ($p<0.05$) higher in Class A patients compared to those of Class B and C, with significantly ($p<0.05$) higher score in Class B patients compared to Class C patients. Mean total scores of other questionnaire domains; fatigue, systemic symptoms, activity and worry, were significantly ($p<0.05$) higher in Class A patients compared to Class C patients, but were non-significantly ($p>0.05$) higher compared to Class B patients. Similarly, the difference between patients of Class B and C was non-significant, but in favor of Class B patients, (Table 4).

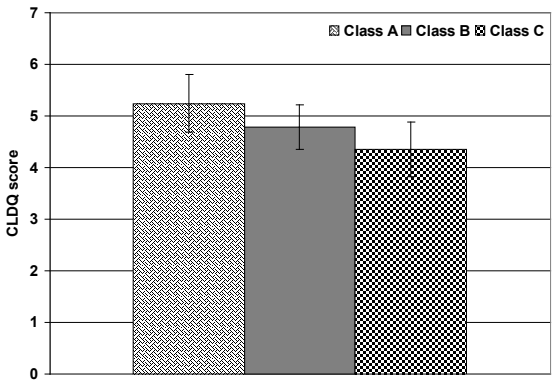

Fig. (2): Mean CLDQ scores of studied patients categorized according to Child-Pugh severity grading of

Table (4): Average scoring of individual items and total CLDQ scoring of studied patients categorized according to CP classification of disease severity

CLDQ domains	CP Class I	CP Class II	CP Class III
Abdominal symptoms	5.42±1.48	5.11±1.17[a]	4.53±0.7[ab]
Fatigue	4.71±1.34	4.31±1.1	4±1.11[a]
Systemic symptoms	5.6±1.27	5.14±1.33	4.89±1.2[a]
Activity	5.4±1.16	4.78±1.27	4.42±1.57[a]
Emotional function	5.13±1.2	4.56±1.11[a]	3.89±0.81[ab]
Worry	5.2±1.22	4.83±1.4	4.42±1.19[a]
Average CLDQ	5.24±0.55	4.79±0.44[a]	4.36±0.54[ab]

Data are presented as mean±SD; CLDQ: Chronic Liver Disease Questionnaire; CP class: Child-Pugh class of disease severity; [a]: significant difference versus CP Class I; [b]: significant difference versus CP Class II

Mean total SFS score of Class A patients was significantly ($p<0.05$) lower compared to that of patients of Class B and C patients with non-significantly ($p>0.05$) lower mean total SFS score recorded in Class B patients compared to Class C patients, (Fig. 3). Scoring of all of the nine individual domains of SFS score were significantly ($p<0.05$) lower in Class A patients compared to Class B and C patients. However, in Class B patients, the mean scores of four domains were significantly ($p<0.05$) lower compared to Class C patients, while the mean scores of the other 5 domains were non-significantly ($p>0.05$) lower in Class B patients of class II compared to Class C patients, (Table 5).

Table (5): Average scoring of individual domains and total FSS of studied patients categorized according to CP classification of disease severity

Fatigue severity scale domains	Class A	Class B	Class C
My motivation is lower when I am fatigued	3.6±1.64	4.67±1.12[a]	5±0.75[a]
Exercise brings on my fatigue	3.6±0.8	4.11±1[a]	4.58±1.1[a]
I am easily fatigued.	3.82±1.51	4.69±1.47[a]	5.47±0.84[ab]

Fatigue interferes with my physical functioning.	3.87±1.63	5±1[a]	5.53±1.12[a]
Fatigue causes frequent problems for me.	3.6±1.16	4.5±1[a]	5.21±1[ab]
My fatigue prevents sustained physical functioning.	3±1.37	4.33±0.89[a]	5±0.88[a]
Fatigue interferes with carrying out certain duties and responsibilities.	2.91±1.62	3.92±1.34[a]	4.47±0.84[ab]
Fatigue is among my most disabling symptoms.	2.18±1	3.31±1.17[a]	3.74±0.93[a]
Fatigue interferes with my work, family, or social life.	2.69±1.06	3.19±0.88[a]	4.1±1.15[ab]
Mean	3.25±0.47	4.19±0.51[a]	4.79±0.26[ab]

Data are presented as mean±SD; CP class: Child-Pugh class of disease severity; [a]: significant difference versus CP Class A; [b]: significant difference versus CP Class B

Patients distribution among high VAFS scores was significantly (p<0.05) higher in Class A patients compared to those of Class B and C with significantly (p<0.05) higher frequency among high scores in Class B patients compared to that of Class C patients. Moreover, mean score on VAFS was significantly (p<0.05) higher in Class A patients compared to that of Class B and C patients with significantly (p<0.05) higher mean score recorded in patients with Class B compared to those of Class C, (Table 6, Fig. 4).

Table (6): VAFS scores of studied patients categorized according to CP classification of disease severity

		Class A	Class B	Class C	Total
Scores	2	2 (4.4%)	3 (8.3%)	5 (26.3%)	10 (10%)
	3	2 (4.4%)	5 (13.9%)	4 (21.1%)	11 (11%)
	4	4 (8.9%)	5 (13.9%)	3 (15.8%)	12 (12%)
	5	7 (15.6%)	7 (19.4%)	3 (15.8%)	17 (17%)
	6	12 (26.7%)	7 (19.4%)	2 (10.5%)	21 (21%)
	7	8 (17.8%)	5 (13.9%)	2 (10.5%)	15 (15%)
	8	7 (15.6%)	3 (8.3%)	0	10 (10%)
	9	3 (6.6%)	1 (2.9%)	0	4 (4%)
	Statistical analysis		X^2=3.447, p_1<0.05[a]	X^2=9.574, p_1<0.01[a]	
				X^2=6.184, p_1<0.05[b]	
Average score		6±1.73	5.17±1.86[a]	3.95±1.72[ab]	

Data are presented as mean±SD; VAFS: Visual analogue fatigue scale; CP class: Child-Pugh class of disease severity; [a]: significant difference versus CP Class A; [b]: significant difference versus CP Class B

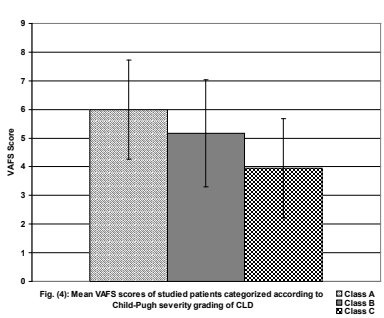

Fig. (4): Mean VAFS scores of studied patients categorized according to Child-Pugh severity grading of CLD

Patients distribution among lower MFIS scores was significantly (p<0.05) higher in Class A patients compared to Class B and C patients with significantly (p<0.05) higher frequency among lower scores in Class B patients compared to that of Class C patients. However, mean total MFIS score was significantly (p<0.05) lower in Class A patients compared to that of Class C patients and was non-significantly (p>0.05) lower compared to Class B patients. Moreover, mean total MFIS score was non-significantly (p>0.05) lower in Class B patients compared to Class C patients, (Table 7, Fig. 5).

Table (7): MFIS scores of studied patients categorized according to CP classification of disease severity

		Class A	Class B	Class C
Scores	<21	7 (15.6%)	4 (11.1%)	2 (10.5%)
	21-<42	31 (68.9%)	17 (47.2%)	8 (42.1%)
	42-<63	6 (13.3%)	12 (33.3%)	5 (26.3%)
	>63	1 (2.2%)	3 (8.4%)	4 (21.1%)
	Statistical analysis		X^2=3.417, p_1<0.05[a]	X^2=17.18, p_1<0.001[a]
				X^2=5.998, p_1<0.05[b]
Average score		33.9±12	39.4±15.4	47.1±20[a]

Data are presented as mean±SD; CP class: Child-Pugh class of disease severity; [a]: significant difference versus CP Class I; [b]: significant difference versus CP Class II

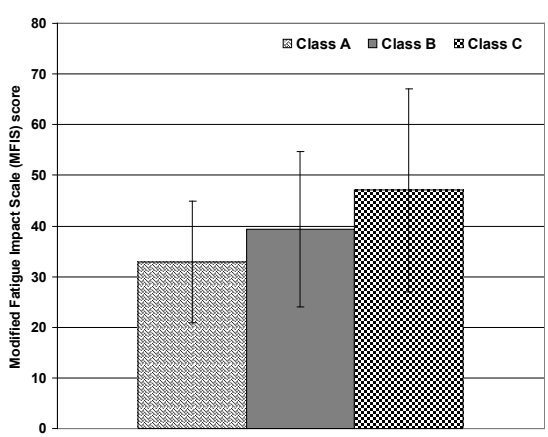

Fig. (5): Mean MIFS score of studied patients categorized according to Child-Pugh severity grading of

Absolute concentrations of estimated neurometabolites showed significant decrease in the three patients' groups compared to control subjects with significantly lower concentration of NAA in Class C patients compared to Class A patients, while the difference was non-significant between Class B patients compared to both Class A and Class C patients. Concerning concentrations of choline and creatine, the difference among patients' groups was non-significant despite being in favor of Class A. Similarly, NAA/Cr and Cho/Cr ratios were significantly lower in patients' groups compared to control subjects with significantly higher ratios in Class A patients compared to Class B and C patients. However, the ratios were non-significantly higher in Class B patients compared to Class C patients, (Table 8, Fig. 6, 7).

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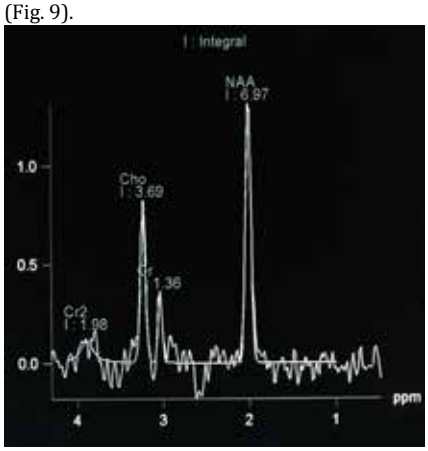
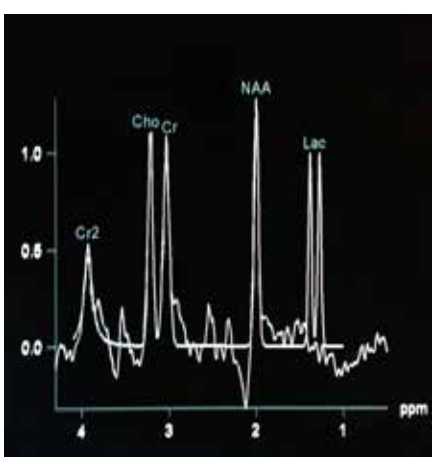
Table (8): Absolute metabolite concentrations and metabolite/creatine peak area ratios

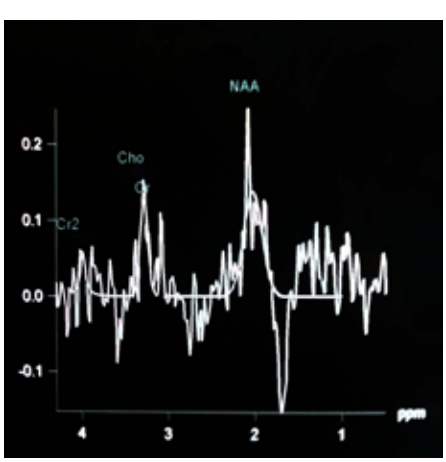
		Control	Class I	Class II	Class III
Absolute concentration	NAA	5.93±0.27	4.358±0.691[a]	4.089±0.631[a]	3.844±0.838[ab]
	Cho	3.32±0.575	2.66±0.585[a]	2.616±0.498[a]	2.396±0.742[a]
	Cr	3.869±0.625	3.405±0.54[a]	3.284±0.687[a]	3.224±0.758[a]
Ratios	NAA/Cr	1.562±0.218	1.358±0.232[a]	1.215±0.198[ab]	1.2±0.07[ab]
	Cho/Cr	0.857±0.045	0.811±0.056[a]	0.767±0.063[ab]	0.744±0.107[ab]

Data are presented as mean±SD; CP class: Child-Pugh class of disease severity; NAA: N-acetyl aspartate; Cho: Choline; Cr: Creatine; [a]: significant difference versus Control; [c]: significant difference versus CP Class I

The relative risk for having high MFIS on having low NAA/Cr is 0.1667 (95% CI: 0.0767 to 0.3621; Z-= 4.527, p<0.0001), (Fig. 8) while the relative risk for having high MFIS on having low Cho/Cr is 0.1333 (95% CI: 0.0578 to 0.3074; Z-= 4.727, p<0.0001), (Fig. 9).







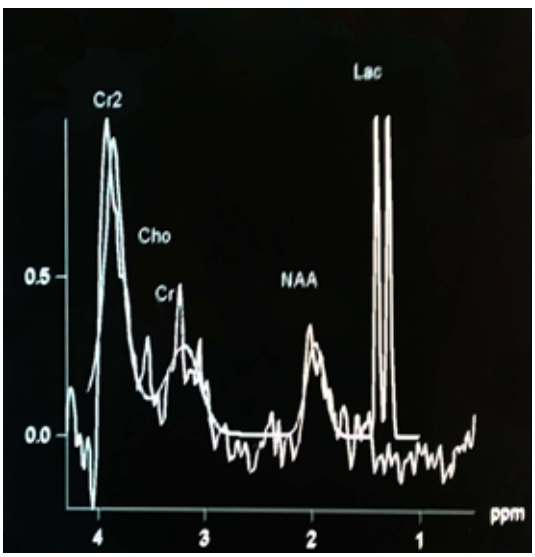


Fig. (6): MRS data obtained in control subjects (a), Class A patient (b); Class B patient (c) and Class C patient (d).

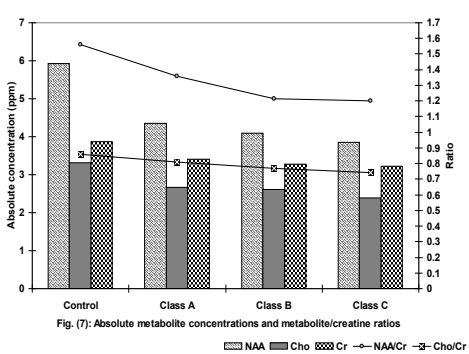


Fig. (7): Absolute metabolite concentrations and metabolite/creatine ratios

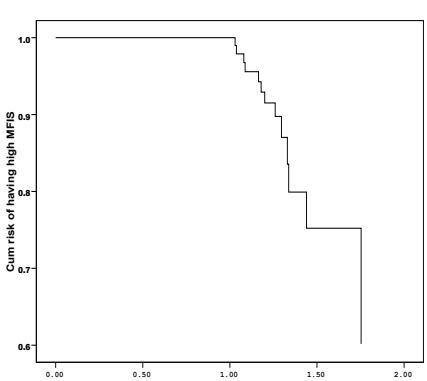


Fig. (8): Cumulative risk for having high MFIS depending on variability of NAA/Cr ratio

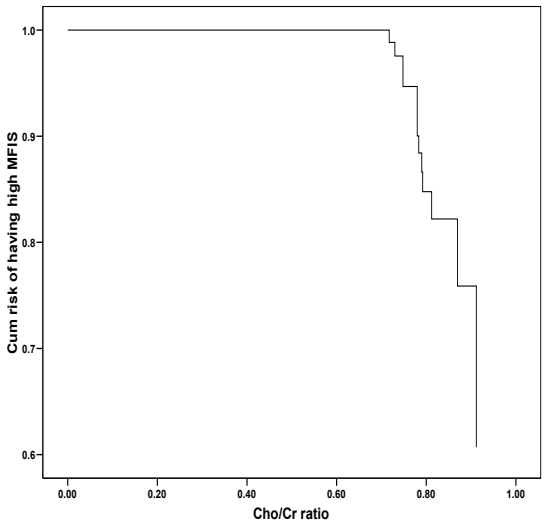


Fig. (9): Cumulative risk for having high MFIS depending on variability of Cho/Cr ratio

Discussion

All enrolled CHC patients showed fatigue of variant extent and was found to be directly related to the extent of deterioration of liver function as manifested by CP classes where patients of Class A showed significantly lower FSS and higher VAFS scores compared to those of Class B with significant difference in favor of Class B on comparison to Class C patients. Moreover, the impact of fatigue on patients' daily life activities as determined by modified fatigue impact scale (MFIS) was significantly higher in Class C patients compared to patients of other classes with significantly more impact in patients of Class B compared to those of Class A.

These findings go in hand with that previously reported in literature; Weissenborn et al. [27] reported the following data concerning their series of CHC patients; all patients had pathological results on FIS, two-thirds of patients showed pathological attention test results, single photon emission computerized tomography detected pathological dopamine and serotonin transporter binding in 60% and 50% of patients, respectively and patients with both decreased serotonin and dopamine transporter binding showed significantly impaired performance in most of the tests applied. Kallman et al. [28] found patients with chronic HCV had greater health-related quality of life (HRQOL) impairment than healthy controls and fatigue was the most important symptom with negative impact on HRQOL up to the finding that about 61% of HCV-infected patients reported fatigue-related loss of activity. Teuber et al. [29] detected a strong negative association between the degree of liver fibrosis and the physical short-form health survey score, also significantly predicting physical HRQOL and the absolute FIS scoring was significantly increased in patients with advanced fibrosis.

Karaivazoglou et al. [30] reported that all aspects of the HRQOL perceived by chronic viral hepatitis patients were significantly impaired compared to the general population, and clinical parameters including infection activity, fibrosis stage or inflammation grade, as well as depressive symptoms and fatigue were found to be significantly associated with impaired HRQOL. Anty et al. [8] found fatigue scores were significantly more elevated in CHC patients than in healthy subjects. Pattullo et al. [31] reported that before receiving treatment, CHC patients had impaired learning efficiency, poorer HRQOL and higher fatigue scores compared with the controls and viral clearance was associated with a significant albeit small improvement in the HRQOL score that did not reach control levels. El-Gindy et al. [9], (2012) found fatigue was present in all their series of CHC patients with a highly significant statistical difference between cases and controls regarding the presence and severity of fatigue.

The MR spectroscopic estimation of neurometabolites detected significant decrease of its absolute concentrations in all CHC patients compared to controls with significantly lower concentration of NAA in Class C patients compared to Class A patients, while the difference was non-significant compared to Class B. Moreover, NAA/Cr and Cho/Cr ratios were significantly lower in patients compared to control subjects with significantly higher ratios in Class A patients compared to Class B and C patients and the relative risk of high FIS was significant on having low NAA/Cr and Cho/Cr ratios.

In line with these data; Weissenborn et al. [32] reported that in comparison to the healthy controls the patients with HCV infection showed evidence of cognitive impairment, primarily attention and higher executive functions, higher levels of anxiety and depression and impairment of quality of life; in addition patients with HCV infection showed a significant decrease of the NAA/Cr ratio in the cerebral cortex on cerebral proton magnetic resonance spectroscopy ((1) H-MRS) while the EEG was slowed in 25% and the deficits were more marked in the patients with moderate rather than mild fatigue.

Winston et al. [33] reported that using (1)H-MRS, right basal ganglia myo-Inosito/Creatine (mI/Cr) ratio in patients with acute HCV in a background of HIV was significantly lower than patients had chronic HIV-1 with no evidence of HCV, and controls with no evidence of HIV or HCV; 50% of acute HCV patients had mI/Cr ratio below the lowest observed ratio in either of the other groups and on neurocognitive testing, there was significant defects in the monitoring domain in acute HCV patients compared to controls. Pattullo et al. [31] found that cerebral (1)H-MRS demonstrated a lower NAA/Cr ratio in the globus pallidus of patients with CHC, which was unchanged with viral clearance.

Bokemeyer et al. [34] reported significant alterations of choline, creatine and NAA concentrations in the basal ganglia in CHC patients compared to controls and found fatigue to be significantly correlated negatively with NAA, choline and creatine and myo-inositol levels in basal ganglia and concluded that HCV infection may induce neuroinflammation and brain dysfunction. Grover et al. [34] demonstrated that positron emission tomography with a ligand for microglial/brain macrophage activation and cerebral (1)H-MRS showed evidence of microglial activation, which positively correlated with HCV viraemia and altered cerebral metabolism in the brains of patients with mild hepatitis C

It could be concluded that fatigue is common CHC associated symptom affecting all patients with varied extent of impact on patients' daily life and could be attributed to altered concentrations of neurometabolites. Modified fatigue impact scale is a useful tool for screening of patients for the presence of fatigue and its impact on life activities and should be implemented as a part of clinical evaluation of CHC patients.

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