Cognitive impairment in patients with hepatitis C and non-hepatitis C non-alcoholic fatty liver disease: Hospital-based study

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Abstract:

Background: Non-alcoholic fatty liver disease (NAFLD) is important cause of hepatic morbidity worldwide. Recently, a significant association between NAFLD and Cognitive dysfunction has been observed.

Objectives: To evaluate the association between NAFLD in patientswith or without chronic hepatitis C virus (HCV) infection and cognitiveimpairment.

Patients and methods: The study included 100 NAFLD participants diagnosed by abdominal ultrasound according to guidelines for the diagnosis and management of non -alcoholic fatty liver disease; 50 of them chronically infected with HCV (Group I) and another 50 patients without chronic HCV infection (Group II). Assessment of cognitive functions was done by the Montreal Cognitive Assessment (MoCA), and Trail Making Test (TMT) (part A and B). Socioeconomic Status assessed by socioeconomic status scale. Magnetic resonant imaging of the brain to calculate periventricular white matter hyperintensities.

Results: 16% of Group I patients were deficient in Trail-A, Trail-B, and MoCA, while 18% of group II patients were deficient in Trail-A, Trail-B, and MoCA. There is a statistically significant negative correlation between body mass index (BMI) and MoCA($r = -0.0243$, p-value = 0.015) and a significant positive correlation between BMI and Trail A($r = 0.276$, p-value = 0.048). Based on the results of multivariate logistic regression analysis, hypertriglyceridemia, and periventricular white matter hyperintensities were predictive for cognitive impairment.

Conclusion: NAFLD, Increased BMI and Hypertriglyceridemia showed significant associations with cognitive dysfunction.

Key words: Cognitive dysfunction, HCV, NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD), an accumulation of excess fat in liver cells that can lead to inflammation, cirrhosis, cirrhosis and liver cancer, is an obesity-related condition that has reached epidemic proportions **(Loomba et al., 2013).**As studied recently, NAFLD is the most common cause of chronic liver disease worldwide, with a 25% global prevalence and a very large clinical and economic burden **(Younossi et al., 2016).** Causes of non-alcoholic fatty liver disease (NAFLD) are hepatitis C virus (HCV), hepatitis B virus (HBV), hyperglycemia, insulin resistance, obesity, etc.The mean prevalence of hepatitis C virus associated NAFLD was 55**%** **(Adinolfi et al., 2016)**. Morbidity and mortality are associated with both liver disease itself and extrahepatic complications associated with NAFLD and metabolic syndrome, particularly cardiovascular disease **(Targher et al., 2016)**.

Cognitive impairment (CI) is one of the most common and challenging conditions in neuropsychology, defined as a decline in intellectual function ranging from a mild form of forgetfulness to severe

and debilitating dementia.**(Robertson et al., 2013).**

Morbidity and mortality are associated with both liver disease itself and extrahepatic complications associated with NAFLD and metabolic syndrome, particularly cardiovascular disease **(Ekstedt et al., 2015).** NAFLD has been reported to be associated with poor performance on cognitive tasks involving attention, executive function, episodic memory, motor speed, and visual constructive skills in people without dementia **(Celikbilek et al., 2018).**In recent years, cognitive dysfunction is increasingly known as a complication of NAFLD because problems with memory, attention, concentration, forgetfulness and confusion have been reported in NAFLD patients with negative effects related to daily life and quality of life.**(Colognesi et al., 2020).** The aim of our study was to evaluate the association between NAFLD with or without chronic HCV infection and cognitive dysfunction.

Patients and methods

This study is a cross-sectional study conducted in the departments of neuropsychiatry and tropical medicine at Qena University Hospital fromDecember 2020 to the end of June2021.

100 NAFLD participants, 50 of whom were chronically infected with HCV (Group I) and another 50 patients without chronic hepatitis C infection (Group II), were included in this study.

The inclusion criteria included: Patients between the ages of 18 and 60 years who were diagnosed as non-alcoholic fatty liver by abdominal ultrasound according to guidelines for the diagnosis and management of non -alcoholic fatty liver disease; **(Van et al., 2011).**

Exclusion criteria included patients with alcoholism, and patients with depression or other metabolic disorders affecting cognition. Patients diagnosed with any type of degenerative or vascular dementia were excluded.

All patients signed awritten informed consent prior to their inclusion in this study and the institutional ethical committee of the Faculty of Medicine, Qena, approved the study (IRB NO; SVU-MED-NAP020-1-20-8-64).

All patients underwent the following:

I. History and Clinical Examination: -

1- Complete history of other medical conditions such as DM, heart disease and kidney failure. History of previous treatment with anti-HCV drugs was also evaluated.

2- Complete clinical examination: It includes assessment of the general condition, vital signsand manifestations of chronic liver disease and Anthropometric parameters were obtained. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

II. Laboratory tests:

1 Complete blood picture (CBC): hemoglobin concentration (Hb%), red blood cells (erythrocytes), white blood cells (WBCs), platelet count.

2 Liver profile: alanine aminotransferase (ALT), aspartate

aminotransferase (AST), albumin, total bilirubin and direct bilirubin, prothrombin time and INR.

3 Fasting blood glucose test, 2-hour postprandial oral glucose tolerance test (OGTT) and HbA1c.

4 Total cholesterol, low-density lipoprotein, very low-density lipoprotein, high-density lipoprotein and triglycerides.

5 HBsAg (Hepatitis B Surface Antigen)

6 Serum HCV Real-Time PCR: Quantitative HCV-PCR was measured using the COBAS Ampliprep/COBAS TaqMan (CAP/CTM) assay with a lower limit of detection of 50 IU.

III. Imaging: - The study patients were subjected to examination using the following procedures:

1. **Abdominal Ultrasound:**Diagnosis of non -alcoholic fatty liver disease is diagnosed by ultrasound using a high - resolution type B ultrasound system by a professional ultrasound physician who at least has 2-year experience in US. The diagnosis was according to guidelines for the diagnosis and management of non -alcoholic fatty liver disease; 2010 update**(Van et al., 2011).**

2. **Brain MRI:** Brain MRI was performed on all patients on a Philips Achieva class II MRI 1.5-T scanner (Philips Medical Systems- Best-Netherlands).The severity of cerebral periventricular white matter hyperintensity (PVWH)was assessed using the Fazekas scoring system. The severity of the PVWMH was graded as either none (grade 0); mild (grade 1; moderate (grade 2); or a marked decrease in the attenuation of white matter (grade 3) **(Fazekas et al., 1987)**.

IV. Cognitive functions were assessed by:

- Montreal Cognitive Assessment (MoCA): The MoCA assesses 8 cognitive domains including attention, concentration, visuospatial/ executive functions, memory, language, abstraction, calculation, and orientation. The total possible score is 30 points; a score of 26 or above is considered normal, while a score of 25 or below indicates impairment **(Nasreddine et al., 2005).**

- Trail Making Test (TMT) (Parts A and B):two parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. Part A assesses visual perception rapidity and psychomotor rapidity. Part B assesses mental shifting and the subject's attention ability. The score for each part is the number of seconds required to complete the task. Trail A between (28-33 seconds) is average and > 78 seconds is deficient. Trail B between (60-84 seconds) is average and > 273 seconds is deficient **(Reitan, 1958).**

IV. Socioeconomic status:

Assessment of the socio-economic status according to Abdel-Tawabsocio-economic status scale, this scale consisted of four dimensions, namely, level of

education, employment, total family monthly income, and lifestyle of the family. **(Abdel-Tawab, 2012).**

Statistical analysis

The data were studied using the Statistical Software for Social Sciences (SPSS) version 18.0. Quantitative data were shown as mean ± standard deviation (M ± SD) while qualitative data were shown as frequency and percentage number (%) and were compared by Student's t-test. Chi-square test was used for comparison non-parametric data. $P < 0.05$ was considered significant.

Results

Baseline characteristics

There was a statistically significant difference between studied groups as regard age. The mean age±SD was 45.42 ±10.17 in non-infected group and 67.82 ±8.12 in HCV group (p-value< 0.0001)(Table 1).This study included 33 (66%) males, 17 (34%) females in the first group, 17 (34%) males and 33 (66%) females in the second group. There was a statistically significant difference (p-value< 0.001) between males and females with respect to seropositive. Hepatitis C virus infection was more positive in male patients (66%) than in females (34%) (Table 2).

There was no statistically significant difference between the studied groups regarding socioeconomic status (Table 3).

There was no significant difference between the studied groups regarding periventricular white matter hyperintensity (PVWH)in brain MRI, we found 32 (64%) patients with normal brain MRI, while 11 (22%) patients had periventricular hyperintensity of white matter (PVWH). -1), followed by 5 (10%) were (PVWH-2) and 2 (4%) were (PVWH-3) for unaffected patients, 34 (68%) were normal brain MRI, followed by 10 were (20%) Of the patients (PVWH-1), 4 (8%) were (PVWH-2) and 2 (4%) patients (PVWH-3) were for the hepatitis C virus-infected group (Table 4).

8 (16%) patients with Trail-A, Trail-B and MoCA deficient in the first group. While the second group includes 9 (18%) patients deficient in Trail-A, Trail-B and MoCA, as shown in Table (5).

There is a significant correlation between BMI and cognitive impairment. Table (6) showed a statistically significant negative correlation between BMI and MoCA($r = -0.0243$, p-value = 0.015), and a statistically significant positive correlation between BMI and MoCA($r = 0.276$, p-value = 0.048) ($r = 0.276$).

Based on the results of multivariate logistic regression analysis presented in Table (7), brain MRI PVWH and hypertriglyceridemia were predictive of cognitive impairment.

Table 1. Age distribution in the studied groups

Variables	Serology	N	Mean	SD	P value
Age	Negative	50	45.42	10.17	**< 0.0001**
	Positive	50	67.82	8.12	

SD: standard deviation

Table 2. Gender distribution in the studied groups

Variables		Gender		P value
		Male	Female	
Serology	**Negative**	17(34%)	33 (66%)	**0.001**
	Positive	33 (66%)	17(34%)	

Table 3. Socioeconomic status in both studied groups

Variables			SES class			P value
			Low	Middle	High	
Serology	**Negative**	**Count**	17	23	10	0.718
		%	34.0%	46.0%	20.0%	
	Positive	**Count**	14	27	9	
		%	28.0%	54.0%	18.0%	

SES: socioeconomic status

Table 4. MRI findings in both studied groups

Variables			MRI Brain				P value
			Normal	PVWH 1	PVWH 2	PVWH 3	
Serology	**Negative**	Count	32	11	5	2	0.974
		%	64.0%	22.0%	10.0%	4.0%	
	Positive	Count	34	10	4	2	
		%	68.0%	20.0%	8.0%	4.0%	

PVWH: periventricular white matter hyperintensity

Table 5. Comparison between studied groups as regard results of cognitive scales

Variables			TMT A		TMT B		MoCA	
			Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Serology	**Negative**	Count	41	9	41	9	41	9
		%	82.0%	18.0%	82.0%	18.0%	82.0%	18.0%
	Positive	Count	42	8	42	8	42	8
		%	84.0%	16.0%	84.0%	16.0%	84.0%	16.0%
P value			0.500		0.500		0.500	

MoCA; Montreal Cognitive Assessment, TMT; Trail Making Test

Table 6. Correlation of study variables to cognitive scales

Variables		Trail A	Trail B	MoCA
Age	r	0.101	0.083	-0.043
	P	0.317	0.411	0.674
AST	r	-0.127	0.071	0.101
	P	0.210	0.485	0.317
Total Bilirubin	r	-0.091	-0.062	0.126
	P	0.366	0.543	0.211
ALT	r	-0.047	-0.001	0.023
	P	0.644	0.993	0.822
Direct Bilirubin	r	0.004	-0.017	0.055
	P	0.971	0.867	0.584

Cholesterol	r	-0.090	0.097	0.137
	P	0.374	0.338	0.173
Triglyceride	r	0.033	-0.003	0.024
	P	0.742	0.979	0.815
HDL	r	-0.063	-0.039	0.073
	P	0.533	0.700	0.468
BMI	r	0.198*	-0.067	-.0243*
	P	**0.048**	0.510	**0.015**
WC	r	0.077	-0.025	-0.021
	P	0.446	0.807	0.833
SES	r	0.003	-0.012	0.004
	P	0.977	0.909	0.968

ALT: Alanine Transaminase; AST: Aspartate Transaminase; BMI: body mass index; WC: waist Circumference; HDL: highdensity lipoprotein; SES: socio-economic status.

Table 7. Multivariate logistic regression analysis for prediction of cognitive impairment

Variables	Trail A		Trail B		MoCA	
	B	Sig.	B	Sig.	B	Sig.
Age	-0.087	0.124	-0.024	0.356	-0.087	0.124
AST	-0.134	0.176	0.043	0.045	-0.134	0.176
Total Bilirubin	-5.382	0.238	-0.383	0.823	-5.382	0.238
ALT	0.086	0.086	-0.014	0.443	0.086	0.086
Direct Bilirubin	6.079	0.532	-1.533	0.650	6.079	0.532
Cholesterol	-0.030	0.082	0.011	0.121	-0.030	0.082
Triglyceride	0.019	**0.049**	-0.002	0.602	0.019	**0.049**
HDL	-0.058	0.470	-0.020	0.603	-0.058	0.470
BMI	0.217	0.125	-0.064	0.447	0.217	0.125
Waist Circumference	0.059	0.378	-0.015	0.706	0.059	0.378
MRI Brain		**0.011**		**0.001**		**0.011**
MRI Brain (1)	-9.871	**0.011**	-3.906	**0.012**	-9.871	**0.011**
MRI Brain (2)	-4.328	0.126	-3.340	**0.041**	-4.328	0.126
MRI Brain (3)	0.656	0.811	-0.402	0.817	0.656	0.811
SES	-0.087	0.592	0.001	0.990	-0.087	0.592
Constant	3.961	0.686	4.367	0.434	3.961	0.686

SES: socioeconomic status

Discussion

The main common cause of chronic liver disease is non-alcoholic fatty liver disease (NAFLD) and it appears worldwide **(Younossi et al., 2016).** Recently, cognitive dysfunction is increasingly recognized as a complication of non-alcoholic fatty liver with negative effects related to quality of life **(Colognesi et al., 2020).**The current study showed through analysis and results that non-alcoholic fatty liver disease is associated with decreased cognitive performance.

The current study showed that chronic hepatitis C patients were older than not infected. The resultsare consistent with national Demographic Health Survey of 2015 in Egypt, that most of infections are

at older age groups in comparison to younger (39.4% versus 11.6%) **(Ministry of Health and Population, Egypt, 2015)**. Drop of new infection in younger ages may be due to strict implementation of national campaign of hepatitis C treatment.

The results of this study are in agreement with a study by Gerberand colleagues as they found that NAFLD was inversely correlated with cognitive scores. Hyperlipidemia showed stronger associations with baseline cognitive scores and was predictive of later cognitive decline **(Gerber et al., 2021).**

Seo and colleagues analyzed data for 4,472 adults aged 20–59 years with NAFLD and Compared to participants without NAFLD, NAFLD participants had lower cognitive performance after controlling for age, gender, race, and education. They concluded that NAFLD was independently associated with lower cognitive performance regardless of cardiovascular diseasesand its risk factors.**(Seo et al., 2016).**On the other hand, Weinstein and colleagues didn't find association between NAFLD and any of cognitive testing **(Weinstein et al., 2019).**The difference may be due to methodological difference between studies including different age groups.

The association between hepatic steatosis and metabolic syndrome including obesity and hypertriglyceridemia is sucha mutual relation as increase BMI and hence lipids ultimately leading to NAFLD. Autophagy is a catabolic process that constitutes turnover of damaged cells, organelles and lipids for degradation in a normal physiological process. Autophagy increased by fasting and starvation. Hepatic lipid specific autophagy decreased in obesity and leading to steatosis**(Yang et al., 2010).**

In the current study, we found that increasing BMI had a negative effect on cognitive performance.Our findings were consistent with **Ariyasinghe et al.(2012) and Rambod et al. (2020)** who observed that obese subjects had lower scores on cognitive tests including MoCA and MMSE than Normal weight subjects. Obesity leads to various cerebral pathological changes such as neuronal injury, global atrophy, accelerated neuroinflammation and atherosclerosis which ultimately leading to cognitive impairment **(Kosakova et al., 2015)**

Multivariate logistic regression analysis showed that higher triglyceride levels were associated with cognitive impairment.The results of the current study are also consistent with the results of other previous studies (**Reynolds et al,. 2010; Lv et al., 2019)** with main finding that association between TG and lower cognitive performance.The finding of the current study showed association with periventricular white matter hyperintensities and cognitive impairment. The findings were consistent with **Jang et al.(2019)** who assessed the relationship between non -alcoholic fatty liver disease (NAFLD) and cerebrovascular disease burden (CSVD)Their findings suggest that NAFLD, and especially fibrotic NAFLD, has a significant association with the presence of cerebral small vessel disease**.**Chronic elevation of the circulating triglycerides promote pro inflammation and affecting processing speed memory and periventricular white matter microstructure irrelevant to other vascular risk factors and have an inverse relationship with cognition **(Frazier et al 2015;Bettcher et al., 2013; Parthasarathy et al., 2017)**.

Conclusion

NAFLD associated with cognitive impairment, increased body mass index, and hypertriglyceridemia are considered as risk factors for cognitive dysfunction in NAFLD. TG and MRI hyperintensities are predictors for cognitive dysfunction.

Study's Limitations

The main limitation of this study was the small sample size, further studies with large sample size was needed in this field.

Authors' contributions

AF, AO, AG, contributed to study concept and design, acquisition of data, draft and revision of the report, statistical analyses, and interpretation of data. AA, and AG contributed to case recruitments, acquisition of data and statistical analyses. AF, AG contributed to editing of this report. All authors read and approvedthe final manuscript.

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