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RESEARCH

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Impact of direct-acting antivirals on neuropsychiatric and neurocognitive dysfunction in chronic hepatitis C patients

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Abstract

Background: Hepatitis C virus (HCV) infection is associated with psychiatric and cognitive dysfunctions. We aimed to investigate depression, anxiety, and cognitive function of chronic hepatitis C (CHC) patients before and after treatment with direct-acting antivirals (DAAs). Forty CHC patients (20 non-cirrhotic and 20 cirrhotic) who had undergone DAA treatment in our outpatient clinic and ten controls. We administered the Hospital Anxiety and Depression questionnaires to measure the anxiety and depression symptoms and the Cognitive Abilities Screening Instruments (CASI) to measure the cognitive function at the beginning and 3 months after the end of the treatment.

Results: Sustained virological response (SVR) was achieved in all patients. Post-treatment anxiety and depression scores showed a significant improvement than pre-treatment ones in CHC patients. Regarding CASI, before and after the treatment, a statistical significance was found in short-term memory ($P=0.001$), concentration ($P=0.033$), abstract thinking and judgment ($P=0.024$), total ($P=0.001$) in non-cirrhotic, Also, an improvement was seen in long-term memory ($P=0.015$), short-term memory ($P<0.001$), concentration ($P=0.024$) and total ($P=0.01$) in cirrhotic. However, these changes were still impaired in post-treated cirrhotic compared to controls.

Conclusions: CHC patients' anxiety, depression, and cognitive function partially improved after DAA therapy. Besides, improving the status of CHC, reversibility of cognitive dysfunction in non-cirrhotic patients may indicate the importance of treatment in early stages of liver disease.

Keywords: Anxiety, Chronic hepatitis C, Cognitive function, Depression, Direct-acting antivirals

Background

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease globally, with cirrhosis and hepatocellular carcinoma (HCC) being the most common complications [1]. Neuropsychiatry manifestations of extrahepatic symptoms of HCV infection are common such as cognitive dysfunctions, sleep disorders, depression, anxiety, and anger/hostility neurological and mental problems [2–4]. Compared to the general population, patients with HCV infection had a greater frequency of psychiatric problems, including substance abuse (36%), and mood disorders (28%) [5].

There are many ways that HCV infection itself can cause psychiatric symptoms. These include inflammatory routes, direct brain neurotoxicity, alterations in metabolic and neurotransmitter pathways, and immune-mediated responses [6, 7].

Also, regarding the mechanism that underline neurocognitive changes in CHC patients, a review article

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suggested impairments in emotional learning, memory and how this ability, together with deficient inhibitory control, are core factors in different psychopathologies. As, these impairments caused dysfunctional behaviours, such as deficit in action control and motor inhibition, that are associated with psychopathological and psychiatric conditions, which are characterized by severe impulsivity problems that can determine significant impairment or distress (due to poor regulation and capacity of control, which can be intensified in the presence of emotional stimuli) and result in neurocognitive change [8]. Other suggested mechanism suggested altered emotion perception due to brain-damaged mainly amygdala and superior temporal sulcus dysfunctions [9]. Also, several studies have in fact provided evidence on the implication of frontal lobe circuitry in altered fear extinction features in mood disorders, defining how abnormalities in the ventromedial region of prefrontal cortex (vmPFC), whose smaller volume and altered activity patterns have been observed in these patients, affect memory and emotional learning capacity [10, 11]. Finally, previous review found the tryptophan–kynurenine metabolic pathway plays the most essential role in tryptophan metabolism, producing various endogenous bioactive molecules. The activation of the metabolic pathway is linked to the pathogenesis of a wide range of diseases [12–17].

Previously used interferon (INF)-based treatments had limited efficacy and high toxicity, as well as a high rate of psychiatric manifestations [18–21] and cognitive abnormalities [22]. Interferon-free therapeutic regimens with direct-acting antivirals (DAAs) have transformed HCV treatment by raising the likelihood of cure; referred to as sustained virological response (SVR) and lowering the time of treatment significantly [23, 24]. There are no flu-like symptoms, depression, or suicidal thoughts associated with DAAs because they are not inflammatory cytokines like IFN and ribavirin (RBV). DAAs have been found to have a milder side effect profile than earlier HCV medications [25] and improved patient-reported outcomes (PROs) [26, 27].

To our knowledge, a few studies have been conducted to examine the effects of DAA medication on individuals with chronic hepatitis C (CHC) and mental problems [28]. The majority of the data came from patient-reported outcomes, which were mostly gathered during observational trials on treatment tolerance and adherence [29–31].

Despite effectiveness studies with DAAs that include patients with psychiatric manifestations [31, 32], few researches have particularly addressed psychiatric symptoms in DAA treatment [33, 34].

With repeated observations at baseline and after 12 weeks post-treatment, this study aims to assess and compare the impact of DAAs on cognitive functions and psychiatric disorders in CHC patients. This is the only study that we are aware of that compares the psychological side effects and cognitive function of DAA treatment in CHC patients, non-cirrhotic and cirrhotic.

Methods

This prospective study comprised 40 treatments naive CHC patients from May 2020 to April 2021. They were admitted to the Tropical Medicine and Gastroenterology Department at Assiut University's Al-Rajhi Liver Hospital in Assiut, Egypt. Patients were assigned to a 3-month regimen of sofosbuvir/daclatasvir for HCV treatment with or without ribavirin. They were separated into non-cirrhotic ($n=20$) and cirrhotic ($n=20$). The control people ($n=10$) were chosen at random from the outpatient clinic and relatives who had been admitted to our hospital. They were found to have no symptoms or indicators of chronic liver disease, no psychological issues, negative hepatitis serological markers (HBs Ag, Anti-HCV), and normal abdominal ultrasonography. They were eligible patients were diagnosed with CHC infection based on persistent or intermittent elevations in serum transaminase levels for more than 6 months with the presence of anti-HCV antibodies and serum HCV RNA [35]. Participants were classified as non-cirrhotic or cirrhotic based on the severity of hepatic fibrosis as determined by clinical findings, fibrosis-4 (FIB-4) score, and imaging including transient elastography (TE, FibroScan, Echosens, Paris, France) [36, 37]. Cirrhosis was determined by FIB-4 score > 3.25 for advanced fibrosis/cirrhosis and TE with a liver stiffness ≥ 12.5 kPa [38].

Child–Pugh classification [39] was used to determine the severity of liver cirrhosis, and those in Classes B and C were excluded from this study. We also excluded patients with non-hepatitis C-related liver diseases, co-infection with human immunodeficiency virus (HIV) or Hepatitis B (HBV), a history of treatment with pegylated interferon or DAAs, hepatocellular carcinoma, pregnancy, comorbid condition, such as diabetes mellitus, hypertension, chronic renal disease, overt hepatic encephalopathy, and other psychiatric or neurological disorders, as well as patients who had undergone liver transplantation.

For 12 weeks, non-cirrhotic group were given DAA therapy in the form of a once-daily oral dose of sofosbuvir (400 mg) and daclatasvir (60 mg) in combination with ribavirin (1000–1200 mg) according to body weight (for cirrhotic group only) based on the protocol provided by the National Committee for Control of Viral Hepatitis in Egypt (National Community College Hispanic Council's (NCCHC)guidelines for the management of adult patients with HCV infection) available According to the

EASL Recommendations for Treatment of Hepatitis C 2016, the combination of sofosbuvir and daclatasvir is still an appropriate option [40–42]. All subjects were followed up 3 months after finishing DAA therapy to assess treatment response and re-evaluate their neuropsychological tests. Non-detectable HCV-RNA in serum at 12 weeks post-treatment (SVR12) was characterized as a sustained virological response (SVR) [43].

The sample size was calculated using G power software version 3.1.3 [44], using ANOVA test for comparing difference in mean of depression score between three independent mean, effect size 0.5(assumed effect size). Difference of between 3 groups under the study), alpha error prob 0.05, power (1-beta error prob) 0.80. The required sample size was total 42 patients and it was raised to 50 patients in each group.

Before beginning DAA therapy, all participants underwent a thorough medical and psychiatric assessment, which included sex, age, residence, marital status, educational level, employment, history of psychiatric illness, medical or neurological disease, and drug history.

Laboratory investigations included complete blood count, liver function tests, HCV antibodies using an Ortho HCV Version 3.0 ELISA (Ortho Diagnostics Systems, Raritan, NJ, USA), and quantitative HCV-RNA using an Artus HCV-RG-RT-PCR kit (Qiagen, Hamburg, Germany) according to the manufacturer's instructions.

All individuals were subjected to Socio-economic Status Scale and neuropsychological tests, including Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, and Cognitive Abilities Screening Instruments (CASI).

Social-economic Status Scale [45]: It was composed of three scores: occupation, education, and social class. The last score comprised three factors: income, crowding index, and sanitation score. The total socio-economic score was 23, with scores of 19 + indicating a high socio-economic standard, 15–19 indicating a middling socio-economic standard, and less than 15 indicating a poor socio-economic standard.

Hamilton Depression Rating Scale (HDS) [46]: It was a clinical rating scale used to determine the severity of depression. The overall score was calculated by adding the scores for each item (0–4) (symptom was absent, mild, moderate, or severe). The range of scores was 0 to 54.

Hamilton Anxiety Rating Scale (HAS) [47]: It was made up of 14 items used to assess and measure the degree of anxiety. Seven items dealt with psychic anxiety, while the remaining seven dealt with somatic anxiety. Each item was assigned to a collection of symptoms categorized by nature and rated on a 5-point scale ranging from 0 (not present) to 4 (very severe), with higher scores indicating more severe anxiety. Anxiety levels varied from 0 to 56 on a scale of 0 to 56.

Cognitive Abilities Screening Instruments (CASI) [48]: It had 25 test items. They tested orientation, old and recent memory, language skills, list-making ability, abstract thinking, and judgment. The CASI total score was calculated by adding the results from each of the nine domains. The total score ranged from 0 to 100. A greater overall cognitive function was indicated by a higher score.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences; version 26 (IBM Corp., Armonk, NY, USA). To describe descriptive data, mean ± standard deviation (SD) or frequencies and percentages were employed. The Chi-square test (χ^2) or Fisher's exact probability test was used to compare categorical variables. The Student's *t*-test and ANOVA were used to analyse quantitative data. *P*-values less than 0.05 were used to evaluate statistical significance.

Results

Forty patients with newly diagnosed chronic hepatitis C (20 non-cirrhotic and 20 cirrhotic) were included. Their mean age was 43.5 ± 10.6 years and male sex was predominant (57.5%). The majority were rural (67.5%), unemployed (65%) and illiterate (55%). In addition, ten healthy controls (five males and 5 females with mean age of 42.9 ± 9.9) were enrolled in the study. Further sociodemographic characteristics of the studied population and their subgroups are summarized in Table 1, where no significant differences regarding age, gender, residence, education, occupation, and socio-economic level were found between different groups.

Those CHC patients received DAA therapy (sofosbuvir and daclatasvir ± ribavirin for 12 weeks), and they were followed up 3 months after the end of therapy, where all of the patients achieved SVR (responders).

Comparison between CHC-non-cirrhotic patients and controls regarding neuropsychological and neurocognitive changes are summarized in Table 2. Before starting the DAA therapy (pre-treatment), both hepatic patients and controls had no symptoms of anxiety or depression as measured by HAS and HDS, however, the mean values of these scores were significantly higher in patients than controls ($P < 0.001$ for both). On the other hand, the mean values of total CASI ($P = 0.012$) and its components including short-term memory ($P = 0.001$), and abstract thinking and judgment ($P = 0.002$) were significantly lower in those patients than controls.

Up to 50% of HCV patients without additional comorbidities had cognitive impairment, and the degree of this

Table 1 The sociodemographic characteristics among studied groups

Variables	Total patients ($n=40$)	Cirrhotic patients ($n=20$)	Non-cirrhotic patients ($n=20$)	Control group ($n=10$)	Statistical test		
					F value	X^2 value	*P* value
Age (years)	43.5 ± 10.6 (24–60)	44.1 ± 10.9 (29–60)	43.8 ± 12.8 (24–60)	42.9 ± 9.9 (28–58)	0.030	–	0.970
Gender; males	23 (57.5%)	11 (55%)	12 (60%)	5 (50%)	–	0.28	0.8
Residence							
Rural	27 (67.5%)	13 (65%)	14 (70%)	4 (40%)	–	2.67	0.23
Urban	13 (32.5%)	7 (35%)	6 (30%)	6 (60%)			
Occupational state							
Unemployment	26 (65%)	12 (60%)	14 (70%)	3 (30%)	–	3.482	0.175
Employment	14 (35%)	8 (40%)	6 (30%)	7 (70%)			
Education level							
Illiterate	22 (55%)	10 (50%)	12 (60%)	3 (30%)	–	3.480	0.481
Primary education	8 (20%)	6 (30%)	2 (10%)	2 (20%)			
Secondary education	10 (25%)	4 (20%)	6 (30%)	5 (50%)			
Socio-economic scale score	11.3 ± 1.2	11.1 ± 1.1	11.7 ± 1.3	13.9 ± 6	1.696	–	0.202

Values are presented as mean ± standard deviation or *n* (%). *F*-value for ANOVA, X^2-value for Chi-square test. *P*-value < 0.05 is significant

impairment was associated with the degree of fibrosis [49]. Chronic HCV infection is typically accompanied with deficits in concentration, attention, working memory speed, and other higher executive functions. Direct neurotoxicity and inflammation [50, 51] as well as hepatic encephalopathy (HE) in cirrhotic patients have been theorized to contribute to cognitive impairment [49, 51]. Following DAAs, on comparison between pre- and post-treatment neuropsychological and neurocognitive changes in non-cirrhotic patients (Table 2), we found that significantly decreasing HAS and HDS scores in post-treated patients ($P<0.001$ for both, Table 2) ($P=0.031$). Moreover, we found significantly raised values of total CASI score ($P=0.001$) and its components including short-term memory ($P=0.001$), concentration/mental manipulation ($P=0.033$) and abstract thinking and judgment ($P=0.024$) in non-cirrhotic patients after receiving DAA therapy (Table 3). Furthermore, these

Table 2 Distribution of depression, anxiety, and cognitive function among non-cirrhotic and control groups

Variables	Pre-treated ($n=20$)	Post-treated ($n=20$)	Controls ($n=10$)	Pre-treated versus controls		Pre-treated versus post-treated		Post-treated versus controls	
				T value	*P* value	*T* value	*P* value	*T* value	*P* value
HDS	6.5 ± 2.1	2.6 ± 1.7	1.2 ± 0.4	7.749	< 0.001	6.450	< 0.001	2.510	0.031
HAS	5.8 ± 1.4	1.7 ± 0.4	1 ± 0.3	9.000	< 0.001	6.082	< 0.001	1.413	0.175
Long-term memory	7.5 ± 2.1	7.8 ± 2.3	9 ± 1.7	1.772	0.093	1.964	0.081	1.327	0.201
Short-term memory	4.4 ± 1.2	5.6 ± 1.4	7 ± 1.7	3.888	0.001	4.609	0.001	2.015	0.06
Attention	6.7 ± 1.3	6.6 ± 1.7	7.3 ± 1.5	0.973	0.343	0.214	0.835	1.034	0.315
Concentration	3.4 ± 1.3	4.7 ± 1.5	4.6 ± 1.8	1.664	0.113	2.512	0.033	0.133	0.895
Orientation	14.8 ± 4.02	15.1 ± 3.9	16 ± 3.2	0.735	0.472	1.000	0.343	0.562	0.581
Language	8 ± 1.8	8.2 ± 1.8	9.1 ± 1.4	1.492	0.153	1.000	0.343	1.226	0.236
Visual construction/ drawing	5.7 ± 3.4	6.4 ± 2.8	7.8 ± 3.5	1.376	0.186	1.909	0.089	0.995	0.333
List generation fluency	7.3 ± 2.2	7 ± 1.6	7.5 ± 1.8	0.223	0.826	0.758	0.468	0.655	0.521
Abstract thinking and judgment	6.5 ± 1.4	7.7 ± 1.9	9.3 ± 1.9	3.734	0.002	2.714	0.024	1.894	0.07
Total CASI	62.3 ± 13.5	65.9 ± 12.1	77.6 ± 13.8	3.132	0.012	3.870	0.001	2.020	0.06

Values are presented as mean ± standard deviation or *n* (%). *T*-value for Student's *t*-test. *P*-value < 0.05 is significant

CASI: Cognitive Abilities Screening Instruments, HAS: Hamilton Anxiety Score, HDS: Hamilton Depression Score

post-treatment increasing values in CASI score and its component were compatible to that of controls where, no statistically significant differences between controls and non-cirrhotic group following DAAs as shown in Table 2.

Before starting the DAA therapy (pre-treatment), despite the mean HAS and HDS values within normal ranges, they were significantly higher in patients than controls ($P<0.001$ for both). In addition, the mean values of total CASI ($P=0.012$) and its components including long-term memory ($P=0.001$), short-term memory ($P<0.001$), attention ($P=0.015$), concentration ($P=0.012$), orientation ($P=0.007$), language ($P=0.003$), and abstract thinking and judgment ($P<0.001$) were significantly lower in cirrhotic patients than controls.

Following DAAs and SVR achievement, HDS and HAS scores had significantly decreased values in post-treated cirrhotic patients versus pre-treated ones ($P<0.001$ for both, Table 3) but these changes were still impaired in post-treated patients than controls ($P<0.001$ for HDS and $P=0.034$ for HAS, Table 3). Furthermore, we found significantly elevated values of total CASI score ($P=0.01$) and its components including long-term memory ($P=0.015$) short-term memory ($P<0.001$), and concentration ($P=0.024$), in cirrhotic patients after receiving DAA therapy (Table 3). However, these post-treatment changes in cirrhotic group were still impaired comparing to controls where, post-treated patients had significantly lower values of CASI ($P=0.02$), long-term memory ($P=0.004$), short-term memory ($P=0.007$), orientation ($P=0.006$), language ($P=0.002$) visual construction/drawing ($P=0.05$), list-generation fluency ($P=0.05$) and abstract thinking and judgment ($P=0.001$) than controls as shown in Table 3.

Discussion

This study aimed to assess and compare the impact of DAAs on cognitive functions and psychiatric disorders in CHC patients. We had two observations at baseline and after 12 weeks post-treatment. Before therapy, cirrhotic patients had higher depression levels than non-cirrhotic patients, but these scores were significantly lower following treatment in both groups. In contrast, anxiety levels were nearly identical before therapy and dropped in both groups after treatment (Figs. 1, 2, 3).

In both cirrhotic and non-cirrhotic groups, anxiety and depression scores reduced markedly after treatment. Anxiety appears to be more sensitive to treatment response in the HCV group. The considerable treatment success with DAAs may be linked to decreased anticipatory anxiety [52, 53].

Treatment with DAAs may permanently eliminate the HCV etiological component [53]. According to prior research, DAAs for example SOF/DCV, SOF/LD, SOF/VEL/RBV, SOF/DCV/RBV or SOF/LDVOBV/PTV/r + DSV regimens are well-tolerated and has high adherence with a low burden of psychiatric side effects [54, 55].

Depression is widespread in CHC patients treated with IFN [21, 22, 56], and antidepressant medicines are

Table 3 Distribution of depression, anxiety, and cognitive function among cirrhotic and control groups

Variables	Pre-treated ($n=20$)	Post-treated ($n=20$)	Controls ($n=10$)	Pre-treated versus controls		Pre-treated versus post-treated		Post-treated versus controls	
				T value	*P* value	*T* value	*P* value	*T* value	*P* value
HDS	7.4 ± 2.1	3.9 ± 1.6	1.2 ± 0.4	10.781	< 0.001	7.000	< 0.001	4.976	0.001
HAS	6.5 ± 1.2	2.3 ± 0.5	1 ± 0.3	11.524	< 0.001	7.584	< 0.001	2.327	0.034
Long-term memory	5.8 ± 2	6.3 ± 2	9 ± 1.7	3.868	0.001	3.000	0.015	3.250	0.004
Short-term memory	2.8 ± 1.8	4.4 ± 2.1	7 ± 1.7	5.203	< 0.001	7.363	< 0.001	3.030	0.007
Attention	5.4 ± 1.6	6.5 ± 0.8	7.3 ± 1.5	2.702	0.015	1.877	0.093	1.472	0.158
Concentration	2.7 ± 0.9	3.3 ± 0.9	4.6 ± 1.8	2.905	0.012	2.714	0.024	1.988	0.068
Orientation	10.4 ± 4.8	10.3 ± 4.8	16 ± 3.2	3.075	0.007	0.429	0.678	3.121	0.006
Language	6.9 ± 1.5	6.9 ± 1.3	9.1 ± 1.4	3.443	0.003	-	-	3.665	0.002
Visual construction/drawing	5 ± 3.6	4.9 ± 1	7.8 ± 3.5	1.753	0.097	0.246	0.811	1.963	0.052
List generation fluency	7.3 ± 1.8	6.3 ± 0.7	7.5 ± 1.8	0.267	0.793	2.023	0.074	1.994	0.062
Abstract thinking and judgment	4.1 ± 1.3	4.4 ± 1.1	9.3 ± 1.9	7.196	< 0.001	1.406	0.193	7.131	0.001
Total CASI	52.4 ± 14.3	54.9 ± 13.9	77.6 ± 13.8	4.013	0.001	3.237	0.01	3.668	0.002

Values are presented as mean ± standard deviation or *n* (%). *T*-value for Student's *t*-test. *P*-value < 0.05 is significant

CASI: Cognitive Abilities Screening Instruments, HAS: Hamilton Anxiety Score, HDS: Hamilton Depression Score

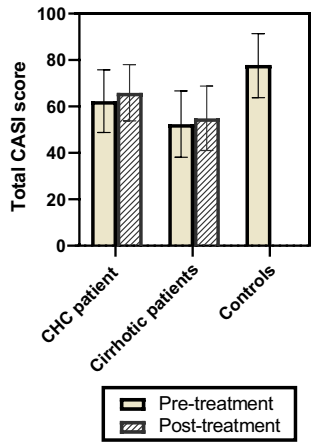

Fig. 1 Total CASI score among the studied groups

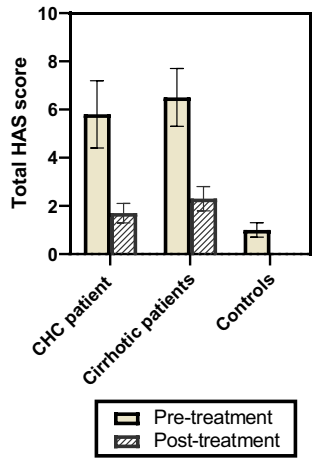

Fig. 2 Total HAS score among the studied groups

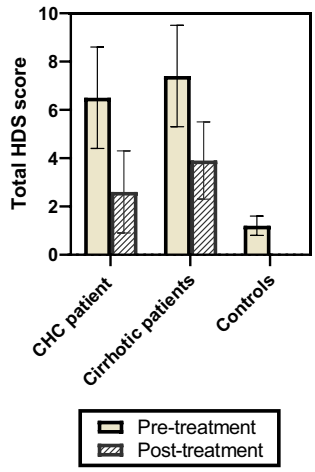

Fig. 3 Total HADI score among the studied groups

known to relieve depressive symptoms in such circumstances [53]. DAA treatment is superior to IFN treatment in terms of avoiding depression [56]. We employed DAA instead of IFN for our patients in this study, removing a well-known risk factor for depression. Regardless of interferon treatment, depression has been identified as a risk factor for HCV patients [53]. The extrahepatic symptoms of HCV in the central nervous system were linked to this connection [57, 58].

In HCV-infected patients, psychiatric problems and emotional distress are widespread. The elimination of HCV may reduce the number of people who require psychiatric care. As a result of treatment with DAA, patients' depression and anxiety levels decreased, and the number of patients requiring psychiatric treatment decreased [53, 59].

As a result, the reduction in depression could be attributed to the absence of HCV in this trial.

Non-cirrhotic patients had significantly lower CASI score and subscales before therapy compared to controls. These scores improved after DAAs and achievement of SVR with significant differences in the mean concentration subscale scores including short-term memory, concentration, abstract thinking and total CASI. On the other hand, cirrhotic patients had lower CASI score and subscales before and after therapy compared to controls. Short-term, long-term memories, concentration, and total CASI all improved after DAA therapy. However, these post-treatment changes in cirrhotic were still impaired comparing to controls including total CASI, long-term, short-term memories, orientation, language, visual construction/drawing, list-generation fluency and abstract thinking and judgment than controls. No statistically significant differences in CASI score and its subscale values between non-cirrhotic group and controls following DAAs indicating that treatment of early stages of CHC patients; non-cirrhotic, is important to regain the normal cognitive function. Our results are compatible with previous studies that documented the efficacy of DAAs in improving cognitive outcomes irrespective severity of liver disease [55, 59–61].

Previous studies have found that chronic HCV infection and non-cirrhotic and cirrhotic liver disease influence brain functions as attention, concentration, and information processing speed even before therapy begins [7, 61–63]. The findings of these studies were unclear as to whether HCV has a direct influence on brain function or if the impairment is mediated by chronic liver illness [22].

The ability to concentrate and the speed of memory processes were significantly impaired in patients with chronic HCV infection compared to healthy controls, according to previously published results suggesting that

HCV-associated neurocognitive decline may be reversible after viral clearance [64]. Healthy controls and previous HCV patients who had eradicated the virus, on the other hand, showed no difference in neurocognitive ability [65].

Similar to other studies suggest that the improvement in several measures of cognitive function after HCV treatment is due to the influence of HCV on cognitive performance rather than psychopathology [22, 61, 66].

In addition, previous researches reported that treatment with sofosbuvir drug and simeprevir or daclatasvir drug improved cognitive performance, especially in relation to memory [55, 60].

In this study, we observed cognitive dysfunction such as impaired concentration in CHC patients. It is worth noting that at the end of the treatment term, all of the patients in this study were PCR negative, indicating an excellent serological viral response. These findings support virological hypotheses for HCV-related cognitive impairment, which suggest that HCV disease processes disrupt brain functions and impair cognition [52].

Several investigations have revealed evidence of HCV replication in the brain, which supports this notion [64, 67].

Furthermore, HCV infection has been linked to a reduction in the generation of brain-derived neurotrophic factor [68, 69]. This factor is hypothesized to be involved in the pathophysiology of cognitive and mood disorders because it plays a critical role in regeneration and neurogenesis [70]. Treating HCV with direct-acting antivirals (DAAs) could improve comorbid psychiatric disorders. However, it would be beneficial to examine the implementation of new therapeutic techniques to treat comorbid psychiatric disorders, such as non-invasive brain stimulation, that operate to ameliorate the symptoms of mental and neurological disorders [71–74].

Limitations and future directions

One of the limitations of this study was the small size of the study population. The follow-up duration was short; longer follow-up durations may provide better knowledge about psychiatric disorders. Prospective cohort studies are needed to evaluate the pretreatment and post-treatment neurocognitive changes that may occur among CHC patients to understand the impact of morphometric and functional cerebral changes in those patients before and after SVR.

In conclusion, CHC patients' anxiety, depression, and cognitive function partially improved after DAA therapy. Besides improving the status of CHC, reversibility of cognitive dysfunction in non-cirrhotic patients may indicate the importance of treatment in early stages of liver disease.

Abbreviations

DAAs: Direct-acting antivirals; CASI: The Cognitive Abilities Screening Instruments; CHC: Chronic hepatitis C; HCV: Hepatitis C virus; INF: Interferon; SVR: Sustained virological response; NCCHC: National Community College Hispanic Council's; HIV: Human immunodeficienc**y** virus; HBV: Hepatitis B virus; HDS: Hamilton Depression Rating Scale; HAS: Hamilton Anxiety Rating Scale.

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None.

Author contributions

GS: recruited participants, analysis, and interpreted data, and were the contributors in writing the manuscript. Gk: wrote the manuscript and analysis of data. EH, AS and SZ: recruited participants, helped in data entry, analyse, and generate result sheets and revised data interpretation and manuscript. NM and KE recruited participants, analysis, and interpreted data, and were the contributors in writing the manuscript. KO: recruited patients and made transcranial vascular assessment. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are available from corresponded on request.

Declarations

Ethical approval and consent to participate

After a detailed explanation of the study's goal, methods, potential dangers, and side effects, each participant gave written informed consent to be included in the study. The Institutional Review Board of Assiut University approved the study protocol on date of October 2014 with authorization number 17200637.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interests.

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