

## Assessment of Cerebrovascular and Cognitive Changes in Chronic Hepatitis C Patients

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### ABSTRACT

**Background:** Hepatitis C viral (HCV) infection is associated with systemic inflammation and metabolic complications that might predispose patients to cerebrovascular atherosclerosis and may report neurocognitive complaints.

**Objective:** This case-control study aimed to assess cerebrovascular and cognitive changes in patients with chronic hepatitis C (CHC) infection.

**Patients and methods:** Transcranial color Doppler assessment of cerebrovascular reactivity and cognitive abilities screening instruments (CASI) was conducted in 100 CHC patients and 100 healthy controls. All enrolled patients were evaluated by Fibroscan and the current study employed a cut-off of  $\leq 12.5$  kPa for excluding cirrhosis.

**Results:** Compared to controls, CHC patients had significantly lower scores on CASI and its components. Patients had significantly lower-middle carotid artery (MCA) intimal media thickening (IMT), peak systolic velocity (PSV), end-diastolic velocity (EDV), and mean flow velocity (MEV) than controls. Additionally, the total CASI score significantly correlated with PSV and EDV of MCA and negatively correlated with IMT, pulsatility index (PI), and resistance index (RI).

**Conclusion:** CHC patients have impaired cognitive function that may be associated with cerebrovascular affection in absence of cirrhosis. Future multi-center studies with the evaluation of the effect of antiviral on cerebrovascular reactivity and cognitive function in such patients are warranted.

**Keywords:** Hepatitis C virus, Cerebrovascular changes, Cognitive function, CASI score, Transcranial color Doppler.

### INTRODUCTION

Hepatitis C virus (HCV) infection is widespread in Egypt. HCV antibodies are thought to be present in 15 to 20% of the general population. Changes in brain functioning in chronic HCV infection patients may manifest long before development to severe liver cirrhosis in the absence of hepatic encephalopathy. Regardless of the severity of the liver illness, roughly half of patients with chronic HCV infection developed neuropsychiatric symptoms, resulting in a worse quality of life <sup>(1,2)</sup>.

Cirrhosis and hepatic encephalopathy are prevalent in persons infected with the Hepatitis C virus, and neurocognitive impairment is widespread (HCV). Neurocognitive impairment has been documented in non-cirrhotic HCV patients, and there have been indications of HCV invasion in the central nervous system (CNS). HCV is considered to enter the CNS by direct viral invasion or indirect neuroinflammation <sup>(3)</sup>.

There have been reports of neurological abnormalities in areas such as the prefrontal cortex, basal ganglia, thalamus, and white matter tracts. Memory, attention, processing speed, and executive skills are hypothesized to be hampered by dysfunction in these frontostriatal networks <sup>(4,5)</sup>. However, the reported incidence of HCV-associated neurocognitive impairment varies widely <sup>(6)</sup>.

The significance of the association between HCV infection and cerebrovascular illness is currently debated. Despite fluctuations in cerebral perfusion, healthy brain arteries may maintain a consistent cerebral blood flow. The primary basal cerebral arteries can be

evaluated noninvasively using transcranial color Doppler (TCCD) <sup>(7)</sup>.

The TCCD calculates the mean flow velocities (MFV) of the major basal intracranial arteries. Parameters related to cerebrovascular resistance are pulsatility index (PI), a measure of the MFV variability, and the resistance index (RI). The current work was designed to evaluate cerebrovascular and cognitive changes in non-cirrhotic HCV-positive individuals.

### PATIENTS AND METHODS

This case-control study was conducted over one-year duration between May 2020 and May 2021. It was performed at the Outpatient Clinic of Tropical Medicine and Gastroenterology Department.

#### Participants

One hundred naïve-treatment patients with chronic hepatitis C (CHC) infection were enrolled. HCV infection was confirmed by positive HCV antibody and HCV-ribonucleic acid positive by polymerase chain reaction. In addition, 100 healthy individuals were enrolled in the study as controls. Patients and controls were matched for age, gender, and socioeconomic status.

Exclusion criteria included; unwillingness to participate, smoking, liver cirrhosis (as confirmed by ultrasound, Fibroscan, and/or endoscopic evidence of portal hypertension), cerebrovascular disease, systemic hypertension, diabetes mellitus, Lifetime diagnosis of a psychotic disorder, use of pharmaceuticals known to affect cognitive functioning, history of neurological

conditions including stroke, neurodegenerative dementia or seizure disorder and/or known metabolic causes of cognitive impairment (e.g. hypo- or hyperthyroidism).

## PATIENTS AND METHODS

All participants were subjected to thorough history taking [age, sex, body mass index, smoking status, occupation, associated comorbidities, socioeconomic status <sup>(8)</sup>] and physical and clinical evaluation.

All patients with HCV infection were subjected to transient elastography (TE) (FibroScan®) to assess fibrosis by measuring liver tissue stiffness which is now standard of care as a noninvasive method of assessing fibrosis in HCV <sup>(9)</sup>.

Typically, a normal range is between 2.4 and 6.5 kPa. Cut-off scores for TE differ depending on the liver condition (e.g. HCV, HBV, non-alcoholic fatty liver disease, alcohol hepatitis), and also varies within the literature itself. In HCV-infected individuals, a cut-off score of 12.5 kPa has a predictive value of 77% and 90% respectively in the diagnosis of cirrhosis <sup>(10)</sup>. The current thesis employed a cut-off of  $\leq 12.5$  kPa for excluding cirrhosis <sup>(10)</sup>.

### Transcranial color Doppler assessment of cerebrovascular reactivity:

In both studied groups; we performed all measurements using the Acuson X500 Ultrasound system (Siemens, Erlangen, Germany) with a P4-2 (2–4 MHz frequency) transducer. The studied subjects were examined during the afternoon in a quiet room while lying in a comfortable supine position without any visual and auditory stimulation after 5 minutes of bed rest.

After the participants' blood pressures were measured, the arteries of the dominant side of the circle of Willis were insonated through the temporal bone window by standard protocol with a special focus on the middle cerebral artery (MCA). Peak systolic velocity (PSV), end-diastolic velocity (EDV), mean flow velocity (MFV), resistance index (RI), and pulsatility index (PI) were measured.

### Cognitive abilities screening instrument (CASI):

Cognitive abilities screening instrument (CASI) <sup>(11)</sup> is a 25-item test that provides a quantitative assessment of memories for past knowledge and present input, attention, concentration, orientation, language or verbal fluency, drawing, visual construction, list-generating abilities, abstract thinking and judgment, everyday problem-solving skills. The total CASI score is the sum of its nine domain scores. The total score ranges from 0 to 100. A higher score means better global cognitive function. The CASI is a common comprehensive screening test of cognitive abilities. It takes 45 - 60 min to administer.

### Ethical considerations:

Written informed consent was obtained from each participant before inclusion in the study after a detailed explanation of the intent of the study, the study procedures, potential associated risks, and side effects. The study was approved by the Local Ethics Committee of Assiut University Hospital (IRB No: 17200637). This work has been carried out following the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

### Statistical analysis

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 16, IBM Corp., Armonk, NY, USA). Quantitative data were expressed as mean  $\pm$  standard deviation (SD) and compared with the Student t-test. Nominal data are presented as number (n) and percentage (%). Chi<sup>2</sup> test was implemented on such data. Pearson correlation was used to correlate between neurovascular and neurocognitive changes. A P-value less than 0.05 was considered statistically significant.

## RESULTS

### Characteristics of studied groups (Table 1):

The mean age of patients was  $43.23 \pm 5.65$  years old while the mean age of controls was  $45.11 \pm 8.11$  years old. The majority of both groups were males. Other data are summarized in Table (1). All baseline data showed no significant differences between both groups ( $P > 0.05$ ).

**Table (1): Baseline data of studied patients**

	Patients group (n= 100)	Control group (n= 100)	P
Age (years)	43.23 $\pm$ 5.65	45.11 $\pm$ 8.11	0.061
Male sex	75 (75%)	81 (81%)	0.304
Body mass index (kg/m <sup>2</sup> )	25.05 $\pm$ 3.45	24.49 $\pm$ 2.98	0.221
Occupation			
None	47 (47%)	49 (49%)	0.772
Employee	53 (53%)	51 (51%)	
Residence			
Rural	76 (76%)	80 (80%)	0.490
Urban	24 (24%)	20 (20%)	
Socioeconomic status scale	11.7 $\pm$ 1.3	13.9 $\pm$ 6	0.273

Data expressed as mean (SD), and frequency (%). P-value was significant if  $< 0.05$ . All data were compared with Chi with exception of age, body mass index, and socioeconomic status scale that were compared by the Student t-test.

**Cognitive function assessment among studied groups (Table 2):**

With exception of visual construction and list generation fluency, all other components of CASI were significantly lower among CHC patients in comparison to controls. Also, the total CASI score was significantly lower among patients than in controls ( $52.4 \pm 14.3$  vs.  $77.6 \pm 13.8$ ;  $P < 0.001$ ).

**Table (2): Cognitive function assessment among studied groups**

	Patients group (n=100)	Control group (n=100)	P
Long term memory	$5.8 \pm 2$	$9 \pm 1.7$	0.01
Short term memory	$2.8 \pm 1.8$	$7 \pm 1.7$	< 0.001
Attention	$5.4 \pm 1.6$	$7.3 \pm 1.5$	0.012
Concentration	$2.7 \pm 0.9$	$4.6 \pm 1.8$	0.143
Orientation	$10.4 \pm 4.8$	$16 \pm 3.2$	0.007
Language	$6.9 \pm 1.5$	$9.1 \pm 1.4$	0.003
Visual construction/drawing	$5 \pm 2.7$	$7.8 \pm 3.5$	0.097
List generation fluency	$7.3 \pm 2.2$	$7.5 \pm 1.8$	0.826
Abstract thinking and judgment	$6.1 \pm 1.5$	$9.3 \pm 1.9$	0.001
Total CASI	$52.4 \pm 14.3$	$77.6 \pm 13.8$	0.001

Data expressed as mean (SD) and compared with Student t-test. P-value was significant if  $< 0.05$ . CASI: cognitive abilities screening instruments

**Transcranial duplex neurovascular changes of MCA among studied groups (Table 3):**

We found that CHC patients had significantly lower IMT, PSV, EDV, and MFV of MCA in comparison to the controls. On the other hand, RI, and PI showed no significant differences between both groups.

**Table (3): Transcranial duplex assessment of MCA among studied groups**

	Patients group (n=100)	Control group (n=100)	P
IMT	$0.84 \pm 0.25$	$0.63 \pm 0.24$	0.046
PSV	$71.5 \pm 26.1$	$103.1 \pm 31.8$	0.035
EDV	$25.6 \pm 10.3$	$33.1 \pm 11.3$	0.043
MFV	$39.6 \pm 14.8$	$50.8 \pm 24.2$	0.012
RI	$0.64 \pm 0.07$	$0.69 \pm 0.06$	0.160
PI	$1.13 \pm 0.21$	$1.24 \pm 0.2$	0.392

Data expressed as mean (SD) and compared with by Student t-test. P-value was significant if  $< 0.05$ . MCA: middle cerebral artery; MFV: mean flow velocity, PSV:

peak systolic velocity, PI: pulsatility index, RI: resistance index

**Correlation between transcranial duplex neurovascular measurements of MCA and CASI among patients (Table 4):**

It was found that total CASI score significantly correlated with PSV, and EDV of MCA and negatively correlated with IMT, RI, and PI of MCA while no correlation was found between total CASI score, and MFD of MCA ( $P > 0.05$ ).

**Table (4): Correlation between transcranial duplex neurovascular measurements of MCA and CASI among patients**

Correlation of total CASI with	r value	P-value
IMT	-0.471	0.036
PSV	0.529	0.045
EDV	0.644	0.044
MFV	0.215	0.109
RI	-0.705	0.023
PI	-0.684	0.029

Data expressed as r value (strength of Pearson correlation) and P-value (significance of correlation and considered significant if  $< 0.05$ . CASI: cognitive abilities screening instruments; IMT: intimal media thickness; MCA: middle cerebral artery; MFV: mean flow velocity, PSV: peak systolic velocity, PI: pulsatility index, RI: resistance index

**DISCUSSION**

Chronic hepatitis C (CHC) includes many extrahepatic symptoms, including neurocognitive impairment, which can impact infected people. Immunological mechanisms, in which the virus's chronic persistence causes the circulation of immune complexes (mixed cryoglobulinemia) and other autoimmune phenomena, and virological structures, which are related to the virus's extrahepatic tropism to other tissues, may be involved in the pathophysiology (12).

The current study assessed cerebrovascular and cognitive changes in CHC patients in comparison to controls. We found that the mean scores of total CASI and its domains were significantly lower in CHC patients than in controls. These findings were partially compatible with that of Kleefeld *et al.* (13) that demonstrated impairment of sustained attention, concentration, working memory, and processing speed using neuropsychological test batteries. These changes happen regardless of the severity of the liver disease, the rate of HCV replication, structural brain damage, or signal abnormalities on conventional magnetic resonance imaging (14, 15).

Lowry *et al.* (16) reported that half of HCV RNA-positive patients had changes in memory, sustained attention, and delayed auditory recognition, as

compared to HCV RNA-negative subjects who had spontaneous viral clearance. **Hilsabeck et al.** (17) showed that maintaining attention and concentration while performing accurately was the most difficult task for non-cirrhotic patients, with 50% taking an abnormally long time to complete the task, 28.9% making a significant number of omission errors, and about 20% performing in the impaired range including attention, concentration, psychomotor speed, visual scanning and tracking, and mental flexibility.

HCV is considered to enter the CNS by direct viral invasion or indirect neuroinflammation (3). HCV-associated neurocognitive impairments exhibit a profile of dominating frontal lobe involvement, with impairment of working memory, processing speed, set-shifting, decision-making, and verbal fluency (4,5).

In line with the current study, several studies stated that CHC patients had increased carotid intima-media thickening (CIMT) compared to controls (18-21). **Olubamwo et al.** (22) reported that HCV infection increased the risk of developing CIMT by about 4-folds. **Osama et al.** (23) explored that CIMT >1mm was significantly more frequent among HCV-positive patients (80%) than HCV-negative patients (32%). Hepatitis C has been characterized in the literature as encouraging the formation and progression of carotid atherosclerosis and increasing the risk of thromboembolic events irrespective of traditional risk factors (18, 22, 24).

Several biological mechanisms have been postulated to explain the link between CHC and increased CIMT via viral load, cryoglobulins (CGs), and steatosis with atherogenic factor regulation such as inflammation (19, 25). HCV-RNA has been found in carotid plaques, suggesting that active local HCV infection is a risk factor for the development of carotid atherosclerosis (25, 26). Moreover, CHC infection may be linked to enhanced foam-cell growth, immunological responses, alterations in lipoproteins, and pro-coagulant activity (27, 28).

Compatible with our findings, **Pavicic Ivelja et al.** (29) revealed that CHC patients had significantly lower average values of peak systolic, end-diastolic, and mean velocity than controls. Also, they found that CHC patients had altered cerebrovascular reactivity that had negative effects on cerebrovascular hemodynamics partially contributing to the increased risk of cerebrovascular disease. **Adinolfi et al.** (30) found that HCV was more prevalent in patients with stroke than in controls and HCV-positive patients with stroke were younger and with fewer cerebrovascular disease risk factors than HCV-negative patients. Unlike our study, some researchers didn't support chronic HCV infection as a risk factor for cerebrovascular disease (31).

In the present work, significant correlations were found between cognitive dysfunctions and cerebrovascular changes. **Casato et al.** (32) demonstrated that cognitive decline in CHC patients was correlated to

an increased occurrence of periventricular white matter high-intensity signals on T2-weighted MRI that likely reflected the occurrence of small vessel disease resulting in chronic hypoperfusion of the white matter and local alteration of the blood-brain barrier. Also, **Solinas et al.** (33) reported that HCV-related brain dysfunction may be associated with white matter neuronal loss, alterations of association tracts, and perfusion. Furthermore, **Masoud et al.** (34) documented that this link was probably related to the pathogenic effects of the chronic inflammatory state induced by HCV infection on the cerebral microvasculature.

Although the above-mentioned data suggest that HCV infection may increase the risk of atherosclerosis and cerebrovascular disease, and hence its association with neurocognitive dysfunction, the number of studies is still insufficient, requiring cautious interpretation of these results.

This work is a single-center study. Therefore, further cohort multi-center studies are recommended to clarify the mechanisms of these cerebrovascular and neurocognitive changes and to evaluate the effects of direct-acting antivirals (DAAs) on cognitive function and cerebrovascular parameters of CHC patients.

## CONCLUSION

Altered cognition functions are frequently found in CHC patients that may be associated with cerebrovascular changes. These changes can occur regardless of the severity of liver fibrosis.

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**Author contribution:** Authors contributed equally to the study.

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