Patients with hepatitis C infection and normal liver function: an evaluation of cognitive function

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ABSTRACT

Purpose of the study Hepatitis C virus (HCV) is associated with neuropsychiatric complaints. Previous studies have associated cognitive alterations with HCV infection but have often included confounding factors in their samples. This study compares the cognitive performance between patients with HCV infection (HCV patients) and a control group while excluding other factors that may cause cognitive impairment.

Study design This cross-sectional study was conducted from March 2010 through June 2011. HCV infected patients and healthy individuals between the ages of 18 and 80 years were considered eligible. The exclusion criteria included well established causes of cognitive impairment such as depression and cirrhosis. Study participants underwent neuropsychological testing involving measures of attention, memory, abstraction, visuoconstructive abilities, and executive function.

Results Of 138 initial patients, 47 were excluded because of their medical records, three refused to participate, 23 did not attend the consultation, and 32 were excluded because of having Beck Depression Inventory (BDI) scores >11. In all, 33 patients underwent neuropsychological testing; however, three were excluded because of having hypothyroidism, and one was excluded because of having a cobalamin deficiency. For the control group, of the 33 healthy individuals that were selected, four were excluded because of having BDI scores >11. Thus, the final analysis included 29 HCV patients and 29 control participants. The groups did not differ in education, age, or gender. No statistically significant differences were found between the groups regarding cognitive performance.

Conclusions In this study using strict selection criteria, there was no evidence of an association between HCV infection and cognitive impairment.

INTRODUCTION

Hepatitis C is caused by the hepatitis C virus (HCV), an RNA virus of the genus *Hepacivirus* and family Flaviviridae. Studies indicate that approximately 60–85% of people exposed to HCV develop chronic infection.[1] Globally, the number of people infected with HCV is estimated to be between 130–170 million, and HCV infection is five times more prevalent than human immunodeficiency virus (HIV) infection.[1] Since the 1989 publication detailing the discovery of HCV, various diseases with different physiopathological and epidemiological bases have been associated, most anecdotally, with chronic HCV infection.[2 3] It is estimated that 40–74% of patients infected with HCV will experience at least one extrahepatic manifestation within their lifetime.[4]

Cognitive changes have been well documented in patients with chronic hepatopathy, most often as a result of hepatic encephalopathy related to uncompensated liver cirrhosis.[5] However, a growing body of evidence has demonstrated that cognitive changes may also occur before the development of liver cirrhosis.[6] Neuropsychiatric symptoms such as 'brain fog', fatigue, and weakness occur in approximately 50% of patients with HCV, independently of the severity of the hepatic involvement. These complaints do not seem to be related to HCV genotype or replication.[7]

Forton *et al* reported the first evidence of brain metabolic changes in patients with HCV, distinct from the alterations found in hepatic encephalopathy.[8] The occurrence of cognitive deficits in this group of patients may be due to the direct action of the virus in the central nervous system (CNS) or indirectly through production of cytokines.[7]

Several studies have suggested that a relationship may exist between HCV and cognitive dysfunction. However, these studies frequently included patients with well established causes of cognitive impairment, such as the use of illicit drugs, interferon, depression, and cirrhosis.[7]

Given the lack of controls for these potential confounding variables in previous studies, broad and rigorous exclusion criteria were employed in this study to avoid the inclusion of individuals with known risk factors for cognitive impairment. The objective of the current study was to compare the cognitive performance in HCV patients and a control group of healthy individuals, while excluding any participants with conditions that might interfere with cognitive performance.

METHODS

Study design

The current study was an observational, cross-sectional study with paired controls.

Inclusion criteria

This study was conducted at the Gaffrée e Guinle University Hospital (HUGG) of Rio de Janeiro, Brazil, from March 2010 through June 2011. The hospital's gastroenterology service reviews about 4800 patients with hepatitis C annually. All HCV infected patients (with detectable serum HCV RNA) who were being tracked in the hepatology outpatient clinic between the ages of 18 and 80 years were considered eligible. The control group was composed of individuals accompanying the outpatients and inpatients at the HUGG who were between 18 and 80 years old.

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Exclusion criteria

Many factors can provoke cognitive changes.[9] Therefore, in an effort to avoid confounding factors, the following exclusion criteria were established: education of less than 4 years; history of encephalic vascular accident, encephalic cranial trauma, dementia, Parkinson's disease, multiple sclerosis, neurodegenerative disease, chronic obstructive pulmonary disease, congestive cardiac insufficiency, other viral infections (HIV, hepatitis B virus (HBV), human T lymphotropic virus (HTLV)), syphilis, significantly compromised liver function, depression, psychiatric illness, illicit drug use, psychotropic drug use, alcoholism, hypothyroidism, cobalamin or folic acid deficiency; and previous or current use of interferon.

Neuropsychological assessment

The cognitive evaluation was performed in a soundproof room under adequate lighting conditions. Two neurologists trained in the administration of neuropsychological tests, who had knowledge of the blood status of the individuals, conducted the cognitive assessment. Study participants were asked about the use of illicit drugs, alcoholic beverages and psychoactive substances 48 h before neuropsychological testing.

The patients underwent neuropsychological testing by answering questions regarding predefined cognitive complaints (poor memory, dispersal/distractibility, difficulty in performing two tasks simultaneously, and difficulty driving) and were given additional space for spontaneous complaints. The following tests were used.

Mini-Mental State Exam

This test is widely used as a brief screening instrument for cognitive impairment. The cognitive functions assessed in this test are attention, calculation, language, praxis, orientation, memory, and attention span.[10] The Mini-Mental State Exam was applied according to the adaptations and recommendations of the Brazilian Academy of Neurology.[11]

Simple Drawing Test

This test assesses visual identification and incidental, immediate, and delayed visual memory. The test sheet comprises 10 drawings. The score indicates the number of correct responses at each step of the test.[12]

Rey Auditory Verbal Learning Test

This test assesses immediate and delayed verbal memory and evaluates the patient's ability to learn. The Portuguese translated and adapted version of the Rey Auditory Verbal Learning Test (RAVLT) was used.[13] RAVLT scores include the sum of the number of words remembered after five repetitions of a list A (A1–A5) and measures of retroactive interference (A6/A5), proactive interference (B1/A1), forgetfulness (A7/A6), and recognition.

Reverse Numerical Order Test

This test is a component of the Wechsler Intelligence Scale for Adults-III (WAIS-III), which is used to investigate working memory. The score indicates the number of numerical sequences that the patient correctly repeats in reverse order.[10]

Direct Numerical Order Test

The number of digits repeated (in forward order) on the WAIS-III provides an easily administered objective measure of the ability to maintain auditory attention for a brief period.[14]

Trail-Making Test

The Trail-Making Test (parts A and B) represents one of the most widely used tests for assessing divided attention. The score is based on the time taken to execute specific tasks. If this time exceeds 5 min, the test is discontinued.[10] The ratio between the execution times of part B and part A provides an assessment of non-verbal executive function.[15]

'A' Random Letters Test

This test assesses sustained attention and consists of a series of random letters among which a target letter appears with greater-than-random frequency. The score is the sum of the number of errors.[14]

Stroop Test

The Stroop Test, as modified by Dodrill, is considered one of the best tests of selective attention.[10] This test evaluates the performance of the individual (ie, time required to complete each of the two parts of the test) and the difference between these times. The test is stopped if the time required to complete either task exceeds 5 min.[10 16]

Boston Naming Test

This test was used in the Brazilian version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD). In this test, 15 designs are presented to the individual. One point is given for each correct answer, yielding a maximum score of 15 points.[10 17]

Verbal Fluency Test

The Verbal Fluency Test of a semantic category (animals) was used to assess verbal executive function. The score is the number of items spoken (excluding repetitions) in 1 min.[12]

Clock Drawing Test

In addition to evaluating non-verbal executive function, this test covers many other cognitive domains, including verbal comprehension, attention, and constructive abilities. The method chosen was that described by Shulman.[18]

Copies of Geometric Shapes (CERAD)

This test is used to assess visuoconstructive skills.[17] The criteria chosen for correction and punctuation have been published by Rosen *et al*.[19]

Symbol Search Test

The Symbol Search Test is a component of the WAIS-III that is used to investigate processing and learning speed. The test is stopped upon reaching 120 s.[20]

Similarities Test

The Similarities Test of the WAIS-III is used to evaluate conceptualisation and abstraction. The individual is asked to identify the characteristic that is shared by two objects or concepts. The test is discontinued after four consecutive errors.[20]

Depression screening

The Portuguese language adapted version of the Beck Depression Inventory (BDI) was used to screen for depression. The BDI has been used in many clinical trials involving patients with HCV.[21–23]

Holtzheimer *et al*[23] reported that the BDI has a diagnostic sensitivity of 91% for depression using the traditional cut-off

point >10 in a population of drug users with HCV. Analysis of the receiver operating characteristic (ROC) curve showed that a cut-off of 11 has a sensitivity of 91% and a negative predictive value of 92%. Low specificity (63%) and low positive predictive (59%) value are among the limitations of using the BDI.

In the Brazilian version of the BDI, scores between 0 and 11 are indicative of the absence of depression.[21] Therefore, to avoid the inclusion of patients with depression in the study (which could result in a type I error), a BDI cut-off point of 11 was used.

Assessment of hepatic involvement

Biopsies performed in the 12 months before the study were considered valid for the evaluation of the degree of hepatic impairment. The aspartate aminotransferase/platelet ratio (APRI) was calculated for all patients. An APRI ≥1.5 indicates the presence of significant fibrosis, whereas levels ≤0.5 indicate the absence of significant fibrosis. Using a cut-off of ≤1.0 allowed us to exclude the presence of cirrhosis with a sensitivity of 89% and a specificity of 75%.[24] The presence of advanced fibrosis or cirrhosis in a liver biopsy sample (F3 or F4 in the METAVIR classification system, respectively) or an APRI >1 defined a significantly compromised liver.

Blood tests

Blood tests were performed on all patients after the cognitive analysis. Serum sodium, thyroid stimulating hormone (TSH), free thyroxine (T4), cobalamin, folic acid, VDRL (Venereal Disease Research Laboratory, syphilis), HIV, HBV, and HTLVI/II tests were analysed.

Data analysis

The Kolmorov–Smirnov test was used to analyse the hypothesis of normality of the sample. Inter-group comparisons were made with the Student t test or the Mann–Whitney test according to the distribution of variables.

Inter-group differences in reporting cognitive complaints and difference in gender were assessed by Fisher's exact test.

All tests were two-tailed and statistical significance was set at $p<0.05$. Data were recorded and analysed using SPSS V.15 for Windows.

Ethical aspects

The research ethics committee of the HUGG approved the study, which adhered to the guidelines of the Helsinki declaration. Study participants completed a free and informed consent form after receiving a detailed explanation of the study.

RESULTS

Study sample

A total of 138 patients met the initial eligibility criteria, and 47 patients were excluded because their medical records contained one or more of the previously determined exclusion criteria (figure 1).

Consultations to apply the BDI were scheduled for the 91 remaining patients. Of these, 23 patients did not attend the consultation, three patients withdrew from participation in the study, and 32 patients received a score >11 on the BDI. The 33 remaining patients underwent neuropsychological testing and blood sample collection. Three patients were excluded because of hypothyroidism, and one patient was excluded because of vitamin B12 deficiency (figure 2).

Thirty-four healthy individuals were chosen for the control group, of whom five were excluded due to BDI scores >11. The control group was assessed following the same criteria of exclusion for the HCV group; however, these individuals were not subjected to serological tests.

Demographic data

There were no statistically significant differences in sex, age, or education level between the HCV and control groups (table 1). There were no statistically significant differences in the reporting of cognitive complaints between the HCV and control groups. Interestingly, 5/29 (17.2%) patients in the HCV group spontaneously reported complaints of fatigue, while none in the control group reported fatigue (table 2).

Genotype 1 was responsible for 22/29 (78.6%) of the infections in the HCV group. A total of 17/29 (58.6%) individuals in the HCV group had liver biopsies performed in the last 12 months. Of these, 5/17 (29%) were classified as F0, 10/17 (58%) as F1, and 2/17 (11%) as F2, based on METAVIR scores. The mean and median APRIs in the HCV group were 0.41 and 0.38, respectively. The source of HCV infection was blood transfusion in 18/29 (62%), an unknown source in 10/29 (34%), and a biological material accident in 1/29 (4%) of the patients with HCV.

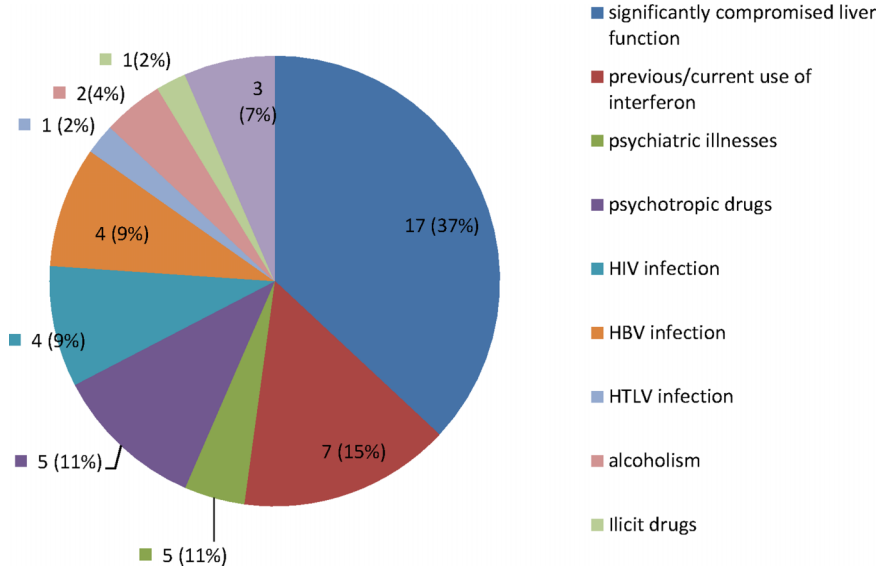

Figure 1 Patients excluded after medical analysis. HBV, hepatitis B virus; HIV, human immunodeficiency virus; HTLV, human T lymphotropic virus. Access the article online to view this figure in colour.

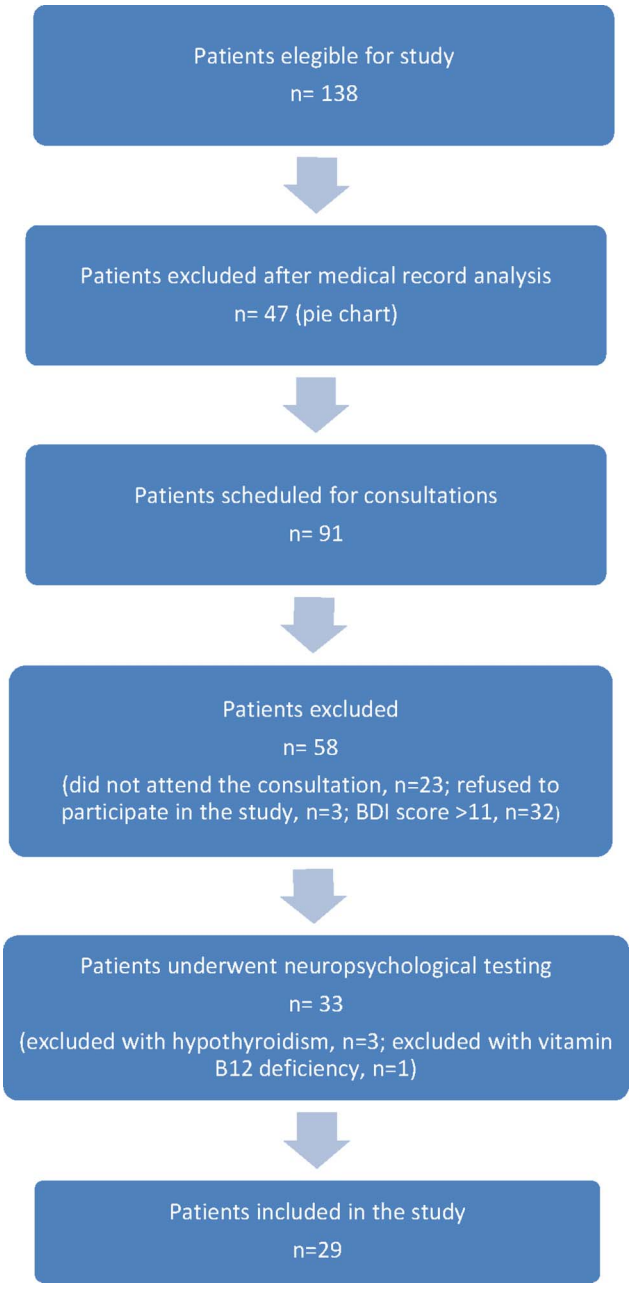

Figure 2 Flow diagram of the selection of patients in the hepatitis C virus group. BDI, Beck Depression Inventory. Access the article online to view this figure in colour.

Table 1 Descriptive statistics for age, education level, and gender

	Group		
	Control (n=29)	HCV (n=29)	p Value
Age (years)			
Mean (±SD)	52.45 (±12.97)	54.10 (±12.23)	Student t test 0.62
Educational level (years)			
Mean (±SD)	9.8 (±4.0)	9.7 (±3.3)	Mann–Whitney test 0.83
Gender	n (%)	n (%)	
Male	14 (48.3%)	11 (37.9%)	Fisher's exact test 0.596
Female	15 (51.7%)	18 (62.1%)	

HCV, hepatitis C virus.

The 23 patients who did not attend the neuropsychological testing exhibited the following characteristics: (1) a mean of 9.2 (±3.2) years of schooling; (2) a mean age of 54.3 (±12.1) years; (3) 12/23 (52.1%) were male and 11/23 (47.9%) were female.

Neuropsychological comparison of the HCV and control groups

Statistical analyses revealed no significant differences between the groups in any of the neuropsychological tests applied (table 3).

DISCUSSION

CNS involvement is observed in many viral infections, and HIV infection is currently one of the most studied. Moreover, the HCV family (Flaviviridae) includes several viruses with known neurotropic effects, such as the West Nile virus, Saint Louis encephalitis virus, Murray Valley virus, and Japanese encephalitis virus.[25] Several hypotheses have been proposed to explain the occurrence of cognitive impairment in HCV infections:

1. *The direct action of the virus in the CNS, through a 'Trojan horse' effect*: The infection of the CNS begins with HCV virus replication in peripheral blood mononuclear cells in the bone marrow, which subsequently serves as precursors of macrophages and microglial cells of the CNS.[7] The production of tumour necrosis factor α (TNFα) and interleukin 8 (IL8) in macrophages/microglia infected with HCV may be responsible for cognitive impairment. However, data about the association between the virus in the brain and impaired cognitive function are still lacking.[7]
2. *The direct action of the virus in the CNS through viral replication in neurons*: Several factors suggest that this is not the case; for example, viral replication is very low within the brain, and HCV RNA is almost undetectable in the cerebrospinal fluid. Moreover, there is no correlation between viral load and cognitive impairment in patients with HCV infection.[7]
3. *A side effect of the inflammatory process*: The cytolytic effects of HCV within the liver activate the immune system. The chronic activation of the inflammatory system results in the production of cytokines, such as IL6, IL4, and TNFα, which are then responsible for the neuronal changes that can result in cognitive impairment.[7]

This study, which was developed with strict selection criteria, indicated no differences in performance on cognitive tests between patients with HCV and the control group. The groups were similar in gender, age, and education, which are known to influence cognitive testing.

Table 2 Cognitive complaints of patients in the HCV and control groups

	Group				
	Control (n=29)		HCV (n=29)		p Value
Complaints	n	%	n	%	Fisher's exact test
Poor memory	13	44.8	13	44.8	1.000
Dispersal/distractibility	9	31.0	7	24.1	0.769
Difficulties in performing 2 tasks	2	6.9	3	10.3	1.000

No participants in either group complained of having difficulty driving.
Regarding other complaints, 5 individuals (17.2%) in the HCV group reported experiencing fatigue.
HCV, hepatitis C virus.

Table 3 Neuropsychological test results for the HCV and control groups

Neuropsychological test	Group	Mean	SD	p Value	Test
MMSE	Control	28.0	1.7	0.407	Mann–Whitney
	HCV	27.4	2.2		
Simple Drawing Test					
Incidental memory	Control	5.9	1.2	0.227	Mann–Whitney
	HCV	6.3	1.4		
Immediate memory	Control	8.7	0.8	0.464	Mann–Whitney
	HCV	8.8	1.1		
Later memory	Control	8.9	1.0	0.385	Mann–Whitney
	HCV	9.1	1.0		
Clock Drawing Test	Control	4.7	0.8	0.288	Mann–Whitney
	HCV	4.2	1.4		
Random Letters Test	Control	0.48	0.74	0.510	Mann–Whitney
	HCV	0.55	0.69		
Stroop Test					
Part 1	Control	116.1	20.3	0.92	Student t
	HCV	116.7	28.9		
Part 2	Control	250.1	45.4	0.70	Student t
	HCV	245.3	49.5		
Part 2–1	Control	137.5	44.9	0.48	Student t
	HCV	128.7	50.5		
Trail-Making Test					
Part A	Control	46.3	17.3	0.109	Mann–Whitney
	HCV	53.7	20.7		
Part B	Control	135.7	74.7	0.586	Mann–Whitney
	HCV	150.96	85.01		
B/A	Control	2.91	1.31	0.565	Mann–Whitney
	HCV	2.82	1.30		
Boston Naming Test	Control	13.9	1.2	0.504	Mann–Whitney
	HCV	14.0	1.3		
Verbal Fluency Test	Control	19.1	5.0	0.66	Student t
	HCV	18.6	5.1		
Digit Span Test					
Direct order	Control	8.0	1.8	0.886	Mann–Whitney
	HCV	7.9	1.7		
Reverse order	Control	4.3	1.9	0.389	Mann–Whitney
	HCV	4.6	2.0		
Geometric Shapes Drawing Test	Control	1.1	1.0		Mann–Whitney
	HCV	1.3	0.9	0.217	
Symbol Search Test					
Correct items	Control	25.4	8.0	0.52	Student t
	HCV	24.1	8.1		
Incorrect items	Control	2.6	2.3	0.770	Mann–Whitney
	HCV	2.9	3.3		
Total	Control	22. 9	8.5	0.47	Student t
	HCV	21.2	9.0		
Similarities Test	Control	18.9	6.4	0.39	Student t
	HCV	17.2	8.1		
Rey Auditory Verbal Learning Test					
Sum of A1-A5	Control	41.9	8.8	0.82	Student t
	HCV	41.3	9.1		
Retroactive interference (A6/A5)	Control	0.84	0.15	0.42	Student t
	HCV	0.80	0.21		
Proactive interference (B1/A1)	Control	0.96	0.57	0.493	Mann–Whitney
	HCV	1.04	0.58		
Forgetting (A7/A6)	Control	0.98	0.13	0.780	Mann–Whitney
	HCV	1.01	0.30		
Recognition	Control	11.6	3.8	0.802	Mann–Whitney
	HCV	11.3	3.5		

HCV, hepatitis C virus; MMSE, Mini-Mental State Exam.

The control group presented higher rates of memory problems (45%) as shown in table 2, which can raise questions about the health state of this group. However, when comparing the means obtained from both groups with the cut-off values suggested on national studies, it was observed that the performance of this group is within the normal range (table 4).[11–13]

Other cognitive tests used in this study were not applied previously in Brazilian studies and therefore not included.

Table 4 Mean obtained in cognitive testing in the study participants and cut-offs in national studies

Cognitive tests	Control group Mean	HCV group Mean	Cut-off in national studies
MMSE	28	27.4	25
Direct order	7.96	7.93	>4
Reverse order	4.31	4.58	>2
Verbal Fluence Test	19.13	18.55	>12
Simple Drawing Test			
Incidental memory	5.86	6.34	>4
Immediate memory	8.65	8.75	>6
Later memory	8.89	9.10	>4
Rey Auditory Verbal Learning Test			
Sum of A1-A5	41.86	41.34	>29.6
Retroactive interference (A6/A5)	0.83	0.79	>0.61
Proactive interference (B1/A1)	0.95	1.04	>0.48
Forgetting (A7/A6)	0.98	1.01	>0.73
Recognition	11.58	11.27	>9.42
Trail-Making Test part A	46.34	53.65	<120

HCV, hepatitis C virus; MMSE, Mini-Mental State Exam.

HCV patients with advanced stages of fibrosis or cirrhosis were excluded because these patients have a high frequency of cognitive impairment. In addition to the hepatic encephalopathy that may occur in patients with significant liver impairment, some patients may have minimal hepatic encephalopathy that is detectable only through neuropsychological testing. The prevalence of minimal hepatic encephalopathy in cirrhotic patients is estimated to be between 30–80%. These patients exhibit cognitive changes that involve executive function, attention span, working memory, and visuoconstructive abilities—symptoms that are frequently reported in patients infected with HCV.[26]

Because of the high prevalence of depression in patients suffering from HCV, a major concern was avoiding the inclusion of depressed participants in this study. Although there is a debate about cognitive impairment in patients with depression, two recent meta-analyses support the presence of cognitive impairment in patients with major depression. These studies demonstrate that executive function and the prefrontral cortex are affected by depression, which may impact cognitive performance.[27 28]

A recent study demonstrated the presence of cognitive changes involving working memory and verbal fluency in patients minor depression.[29] Various studies have reported cognitive changes in HCV infected patients that include deficits in attention, psychomotor speed, working memory, and executive function; this pattern of frontal–subcortical cognitive dysfunction is similar to that found in patients infected with HIV. However, the inclusion of depressed patients in these studies may invalidate the assumption of an association between HCV and cognitive deficit.

Conversely, the high rates of depression reported in patients with HCV may be a neuropsychiatric manifestation resulting from the direct or indirect action of the virus in the CNS. Therefore, the exclusion of these patients may have resulted in selection bias toward patients with fewer cognitive manifestations of HCV infection.

Other factors that may affect cognitive performance in some studies of HCV patients is the inclusion of patients with a history of alcohol and/or illegal drug abuse, and the inclusion of patients using psychotropic drugs or interferon. Lack of rigorous selection criteria in previous studies may have resulted in an overestimation of the prevalence of cognitive impairment associated with HCV.

This study has the following limitations: (1) it was not a longitudinal study, which limits the authors' hypothesis that the association may not exist; (2) the number of study participants was small, thus limiting the statistical power of the study; (3) the control group was composed of persons accompanying the patients—these individuals may experience anxiety disorder due to the health conditions of those patients, resulting in a negative impact on cognitive performance; (4) the control group did not undergo blood testing—thus, one cannot exclude the presence of comorbidities such as subclinical hypothyroidism that can alter the performance in cognitive assessment; (6) the examiners were not blinded to the serological status of the participants, which may influence the outcome of testing; (7) self-reporting is not the most reliable way of ensuring participants did not use illicit drugs or alcoholic beverages—the inclusion of these individuals may have had an impact on the neuropsychological tests; (8) the use of the BDI as a screening tool for depression may have resulted in the exclusion of individuals without depression, due to its low specificity.

In this study there was no apparent relationship between HCV in patients without liver dysfunction, and cognitive impairment. Further studies with greater numbers of participants followed up prospectively over at least 12 months, with careful consideration for potential confounders including depression in the outcome variable analysis, are required to answer the question of a causal association between HCV and cognitive impairment in patients without liver dysfunction.

Main message

In this study there is no evidence of cognitive dysfunction in hepatitis C virus carriers without comorbidities.

Current research questions

Prospective studies with large numbers of participants, with careful consideration for potential confounders, are necessary to establish the relationship between HCV infection and cognitive impairment.

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Contributors JA performed neuropsychological testing, developed the study design and wrote the article. DST collaborated on neuropsychological testing. CEBdeM guided in preparing the study design.

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Competing interests None.

Patient consent Obtained.

Ethics approval The research ethics committee of the Gaffrée e Guinle University Hospital approved the study according to the guidelines of the Helsinki Declaration. Study participants completed a free and informed consent form after receiving a detailed explanation of the study.

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