Chronic HCV infection and neuropsychiatric dysfunction

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1. Introduction

The World Health Organization estimated that in 2015 approximately 130–150 million people were living with HCV infection worldwide, accounting for 1% of the population, and that approximately 399.000 people die each year from hepatitis C [1]. Numerous extrahepatic manifestations were attributed or are more frequent during HCV infection [2–4]. Extrahepatic manifestations occur during chronic infection or cirrhosis and may result in a wide variety of clinical manifestations that may aggravate the clinical spectrum of liver infection or even dominate the clinical picture [4,5]. Studies have revealed that 38–76% of patients with chronic HCV infection develop at least one extrahepatic manifestation [2,3] and among these neuropsychiatric disorders have been reported in series of patients with no signs of overt hepatic encephalopathy (HE). Studies conducted in the last 20 years describe changes in the cognitive performance of HCV-infected patients that emerge long before any evidence of hepatic dysfunction [6–11]. Attention deficits, slowed psychomotor speed, impaired visual construction, scanning and tracking and memory recall have been reported in some patients. Forton et al. and McAndrews et al. found cerebral metabolic alterations in HCV patients (increase in choline and reduction of *n*-acetyl-aspartate) in brain white matter in patients with no signs of overt HE [7,10]. However, not all the studies conducted have detected cognitive abnormalities in HCV patients and some have questioned this association [12,13].

Patients with cirrhosis or portosystemic shunts who have subtle cognitive dysfunctions that cannot be detected by standard clinical examination, but which are evident only during complex tasks performance, are considered to have minimal hepatic encephalopathy (MHE). Prevalence rates of MHE ranges from 30% to 84% in cirrhotic patients [14]. MHE is characterized by changes in selective attention, information processing speed, visual perception, visual construction, fine motor skills and coordination, while general intelligence and language are preserved [15].

This study aimed to identify changes in cognitive function and symptoms of anxiety, depression and hopelessness in treatment-naïve patients with chronic HCV infection and no signs of overt HE, and to verify whether there is a relationship between the possible alterations and viral genotype, viral load and severity of hepatic fibrosis.

2. Methods

Seventy-six adult patients, 40 women and 36 men over 18 years of age, with chronic HCV infection were referred for neurological evaluation from the Division of Infectious and Parasitic Diseases of the Hospital das Clínicas of the University of São Paulo Medical School (HC-FMUSP). These patients had no signs or symptoms of overt liver failure and were antiviral treatment naïve. Patients with positive serological reactions to acquired immunodeficiency virus (HIV), hepatitis B (HBV) or syphilis were excluded. All patients signed the Free and Informed Consent Form, according to the HC-FMUSP Ethics Committee model.

The patients were stratified into age groups with ten-year ranges and by educational level (illiterate, 1–4 years of education, 5–8 years, 9–11 years and 12 years or more). The patients were compared to a population of 78 control individuals, comprising 43 women and 35 men. The controls were HCV, HVB, HIV and syphilis-negative subjects recruited from among companions, spouses, relatives of the study patients, relatives and caregivers of HCFMUSP patients, and unaccompanied volunteers for any illness in the institution and all signed the Free and Informed Consent Form, according to the HCFMUSP Ethics Committee model. The controls were stratified into age groups and educational level corresponding to that of the HCV patients.

HCV patients and control subjects were submitted to anamnesis, clinical examination, neurological examination, brief cognitive evaluation and mood, anxiety and hopelessness evaluation. The screening instruments used for the evaluation were those routinely used in clinical practice and consisted of the following tests:

- Mini-Mental State Examination (MMSE) [16,17].
- Clock Drawing Test (CDT): the scoring methods of Sunderland et al. (1989) and Shulman (2000) were adopted [18,19].
- Verbal Fluency Test in the semantic category – animals [20].
- Digit Span Test (Wechsler Adult Intelligence Scale (WAIS-III) in direct (DO Dig) and inverse order (IO Dig) [21].

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Mood, anxiety and hopelessness were evaluated using the Beck Depression Inventory, Beck Anxiety Inventory and Beck Hopelessness Scale (Beck et al., 1961), applied by an accredited psychologist [22].

Liver biopsies were ordered by the Infectious and Parasitic Diseases Division of HCFMUSP and analyzed by the Anatomical Pathology Division of the same institution. Fibrosis and inflammation grade in liver anatomopathological studies performed before October 2010 were classified according to the 2000 Classification of the Brazilian Society of Pathology and converted to the METAVIR classification according to the approximate equivalence conversion table of the Brazilian Society of Pathology [23]. Only results from liver anatomopathological studies performed < 18 months before the initial study interview were considered in this study. Control group participants underwent laboratory analysis for inclusion in the study.

The software used for the data analysis was SPSS 20 (Statistical Package for the Social Sciences). The tests used were: Chi-square test, Pearson Correlation (Pearson Correlation), Spearman's rho, logistic regression; descriptive statistics (mean, standard deviation); Independent Samples Mann-Whitney U test; Wilcoxon Signed Rank test and Stepwise Multiple Regression.

3. Results

A total of 76 patients with chronic HCV infection and 76 control individuals were included in the study between August 2009 and November 2016. The demographic characteristics of the study population are shown in Table 1. There were no statistically significant differences between the groups in gender distribution ($p = .826$), mean and median age ($p = .761$) or educational levels ($p = .762$).

Data on HCV genotypes, fibrosis and inflammation grades found in the anatomopathological study of the liver, history of drug and/or alcohol abuse in the patient group are given in Table 2.

The Mann-Whitney test showed that there were no statistically significant differences between HCV patients and the control subjects in the distribution of global scores on the cognitive evaluation tests (Table 1). The same lack of difference was found when comparing only subjects with five or more years of education.

Analysis of the MMSE subtests are shown in Table 3. There was a

Table 2
Hepatic fibrosis, genotypes and patients background.

Variable		n	%
Fibrosis grade	F0	12	15.8
	F1	27	35.5
	F2	15	19.7
	F3	6	7.9
	F4	3	3.9
	ND	13	17.1
Inflammation grade	A0	1	1.3
	A1	26	34.2
	A2	26	34.2
	A3	10	13.1
	NR	13	17.1
HCV genotype	1	58	76.3
	2	2	2.6
	3	12	15.8
	1a/2	1	1.3
	5	1	1.3
	X	2	2.6
Alcohol use	Mild	17	22.4
	Moderate	10	13.2
	Heavy	4	5.3
Injectable drug abuse		4	5.3
Both		6	7.9
Alcohol use only		13	17.1
Drug abuse only		4	5.3
Both		18	23.7
No information available		4	5.3

n: number of patients.
X: unknown.
F: fibrosis grade (METAVIR).
ND: not done.
A: inflammation grade (METAVIR).

statistical difference between the groups in memory recall (Pearson X^2, $p = .009$) and attention and calculation ($p = .037$), but on the multivariate analysis only memory recall differed significantly between patients and controls ($p = .023$).

Eighteen patients and 14 controls scored less than was expected for their schooling in the MMSE. The difference was not significant

Table 1
Demographic characteristics of study participants and cognitive assessment results.

	Patients				Controls				
	$n = 76$	Mean(SD)	Min-max	Median	$n = 76$	Mean(SD)	Min-max	Median	p
Gender (% women)	52.6				56.6				0.826
Age (years)		50.8 (11.3)	28–77	51		51.1 (12.0)	25–72	52	0.761
Educational level (years)		8.4 (4.0)	0–15	10		8.6 (3.8)	0–15	9	0.762
MMSE		27.7 (2.9)	20–30	29		28 (2.5)	17–30	29	0.758
Semantic VF		17.3 (5.2)	7–33	18		17.8 (6.3)	7–39	17.5	0.959
CDT		8.4 (1.9)	0–10	9		8.2 (1.8)	1–10	8.5	0.281
DO Dig		5.9 (1.3)	3–9	6		6.0 (1.3)	3–9	6	0.394
IO Dig		4.1 (1.3)	0–8	4		4.0 (1.3)	2–7	4	0.464
BDI		11.7 (9.3)	0–40	9		10.6 (9.1)	0–51	8	0.332
BAI		10.3 (10.0)	0–63	8		9.8 (10.0)	0–50	8	0.459
BHS		4.2 (3.9)	0–17	3		3.9 (3.1)	0–15	3	0.803

n: number of subjects.
SD: standard deviation.
Mann-Whitney.
p: p value.
CDT: clock drawing test.
Min-max: minimum-maximum.
DO Dig: digit test in direct order.
MMSE: Mini-Mental State Examination.
BDI: Beck Depression Inventory.
IO Dig: digit test in inverse order.
BHS: Beck Hopelessness Scale.
BAI: Beck Anxiety Inventory.

Table 3
MMSE subtest scores of patients and controls.

	Patients		Controls		Logistic regression	Multivariate analysis
	Normal	Abnormal	Normal	Abnormal		
	n	n	n	n	p	p
Total score	58	18	62	14	0.426	0.736
Temporal orientation	72	4	70	4	0.567	0.493
Attention/calculation	51	25	47	29	0.037*	0.947
Short-term memory	75	1	75	1	1.0	1.0
Recall memory	42	34	56	20	0.009**	0.023*
Pentagons drawing	57	19	61	15	0.436	0.438
Sentence writing	63	13	61	15	0.676	0.677
Verbal command	76	0	73	3	0.8	0.81
Repetition	76	0	75	1	0.316	0.317
Reading	76	0	74	2	0.155	0.156

n: number of participants.
p: p value.
Pearson X^2.

($p = 426$). The consistency analysis showed that more patients than controls (39% vs 14.5%) fell within the MMSE score range ≤ 23 (Pearson X^2, p = 025). However, when adopting education-adjusted cut-offs for each patient and control, the difference between the groups was not significant. The mean age of subjects with MMSE scores ≤ 23 was 54.2 years (SD: 10.6) in the HCV group and 67.7 years (SD: 3.21) in the control group.

The mean number of words produced on the semantic VF test was 17.3 (SD 5.19) for the HCV patients and 17.8 (SD 6.25) for the control subjects. Ten patients (13.2%) and nine controls (11.8%) had lower VF than expected for educational level. The Wilcoxon test showed no statistical differences on semantic VF between matched samples of patients and controls ($p = .91$). The consistency analysis showed that 96.1% of patients fell within the range of VF ≤ 24 versus 86.8% of controls. Adopting a cut-off value of < 25 words, the difference between patients and controls was statistically significant ($p = .049$) even when adjusting for educational level.

The scores obtained by the study subjects on the CDR, according to the Sunderland score criteria, are shown in Table 4. The distribution of scores was similar between the groups (Mann Whitney, $p = .281$). The mean scores obtained by HCV patients and controls are shown in Table 1. Comparison of patients' performance on the CDT using the Sunderland and Shulman criteria showed no statistically significant difference (Mann Whitney, $p = .526$), and likewise for performance of controls (Mann Whitney, $p = .928$). The Wilcoxon test showed no significant differences between HCV patients and controls ($p = .333$) on the CDT. On the consistency analysis, 34.2% of patients fell within the range of CDT scores of ≤ 8 versus 50% of controls, an unexpected inconsistent result, i.e. controls performed worse on the CDT than patients. When considering only the results of subjects with more than four years of education, there were no significant differences in the distribution of scores between the two groups (Mann Whitney, $p = .052$), with the same result seen on the Pearson X^2 test ($p = .064$).

The results of the DO Dig and IO Dig tests are shown in Table 4. The mean scores obtained by HCV patients and controls are given in Table 1. Pearson's X^2 test also showed no significant difference between the groups on the DO Dig test ($p = .650$) and IO Dig test ($p = .563$). In sample matching, the Wilcoxon test showed no difference between patients and controls on the DO Dig test ($p = .737$) or the IO Dig test ($p = .365$).

The levels of depression, anxiety and hopelessness of the study subjects are given in Table 4. The mean scores obtained by HCV patients on the evaluation of depressive symptoms (BDI), anxiety symptoms and hopelessness symptoms are shown in Table 1. There were no significant differences between groups regarding depressive ($p = .390$),

Table 4
Performance of HCV patients and controls on cognitive screening and Beck Inventory.

		Patients		Controls	
		n	%	n	%
Performance VF	Normal	66	86.8	67	88.2
	Low	10	13.2	9	11.8
CDT performance impairment	None	51	67.1	39	51.3
	Mild	14	18.4	24	31.6
	Moderate	9	11.8	12	15.8
	Severe	2	2.6	1	1.3
Direct order digit test	≤ 4	8	10.5	8	10.5
	≤ 3	1	1.3	2	2.6
	< 3	0	0,0	0	0
Inverse order digit test	≤ 3	23	30.3	29	38.2
	≤ 2	5	6.6	8	10.5
	< 2	1	1.3	0	0
Depression (BDI)	None or minimal	42	55.2	42	55.2
	Mild	17	22.4	24	31.6
	Moderate	12	15.8	7	9.2
	Severe	5	6.6	3	4.0
Anxiety (BAI)	None or minimal	46	60.5	54	71.1
	Mild	20	26.3	11	14.5
	Moderate	8	10.5	6	7.9
	Severe	2	2.63	5	6.6
Hopelessness (BHS)	None or minimal	52	68.4	53	69.7
	Mild	17	22.4	16	21.1
	Moderate	4	5.3	6	7.9
	Severe	3	4.0	1	1.31

n: number of subjects.
VF: verbal fluency.
BDI: Beck Depression Inventory.
BAI: Beck Anxiety Inventory.
BHS: Beck Hopelessness Scale.

anxiety ($p = .185$) and hopelessness ($p = .666$) symptoms. Considering only patients and controls without depression or with any depression grade, the differences between groups were also not significant ($p = .137$) [Table 4]. A greater proportion of patients than controls had symptoms of severe to moderate depression (22.4% vs 13.2%), a difference that did not reach statistical significance (p = .137).

The correlations between the variables studied are in Table 5. BAI scores correlated with gender (higher for female patients). History of alcoholism correlated with BAI scores ($p < .01$), gender (men reporting more alcoholism) and history of drug abuse ($p < .001$). History of drug abuse correlated with gender (p $< .01$), affecting more males than females. HCV genotypes were not correlated with any other variables. (Table 5).

Table 5
Correlations between the variables found in HCV patients.

Variable	Variable	coefficient	p
Educational level	MMSE	0,533	< 0,01
Educational level	Sem VF	0,391	< 0,01
Educational level	CDT	0,471	< 0,01
Educational level	IO Dig	0,413	< 0,01
MMSE	Sem VF	0,434	< 0,01
MMSE	CDT	0,584	< 0,01
MMSE	IO dig	0,424	< 0,01
CDT	IO dig	0,394	< 0,01
DO dig	Sem VF	0,331	< 0,01
DO dig	IO dig	0,639	< 0,01
IO dig	Sem VF	0,471	< 0,01
IO dig	DO dig	0,639	< 0,01
BDI	BAI	0,504	< 0,01
BDI	BHS	0,493	< 0,01
BAI	BHS	0,320	< 0,01
Fibrosis grade	Inflamation grade	0,593	< 0,01
Fibrosis grade	Age	0,349	< 0,01
Alcoholism	Drug abuse	0,380	< 0,01
Educational level	DO dig	0,292	< 0,05
MMSE	DO dig	0,233	< 0,05
CDT	Sem VF	0,256	< 0,05
BDI	Age	0,247	< 0,05
Alcoholism	Gender	0,386	< 0,01
Drug abuse	Gender	0,450	< 0,01
DO dig	Fibrosis grade	0,326	< 0,05
Gênero	BAI	−0,313	< 0,01
Idade	Sem VF	−0,348	< 0,01
Educational level	Age	−0,450	< 0,01
Educational level	BDI	−0,357	< 0,01
Alcoholism	BAI	0,313	< 0,01
Age	MMSE	−0,260	< 0,05
MMSE	BDI	−0,282	< 0,05
MMSE	BHS	−0,23	< 0,05
Sem VF	BDI	−0,248	< 0,05
CDT	Age	−0,256	< 0,05
CDT	BDI	−0,241	< 0,05
IO dig	BDI	−0,235	< 0,05
BDI	Sem VF	−0,248	< 0,05
BDI	IO dig	−0,235	< 0,05
Viral load	Fibrosis grade	−0,291§	< 0,05

Coefficient: Pearson's coefficient correlation.
MMSE: Minimental State Examination.
Sem VF: seemantic verbal fluency.
BDI: Beck Depression Inventory.
CDT: clock drawing test.
BAI: Beck Anxiety Inventory.
DO dig: direct order digit test.
BHS: Beck Hopelessness Scale.
IO dig: indirect order digit test.
Fibrosis grade: hepatic fibrosis grade (METAVIR).
Inflamation grade: hepatic inflamation grade (METAVIR).
§: Spearman's rho coefficient.

4. Discussion

In our study, 23.7% of the patients had lower than expected MMSE scores for educational level. McAndrews et al. and Kramer et al. found lower rates of cognitive impairment of 13% and 16% in patients, respectively, despite using more sophisticated instruments for neuropsychological evaluation [10,24]. The percentage of patients with cognitive impairment in the present study was lower than the 38% found by Hilsabeck et al. and 33% by Fontana et al. [9,25]. Mapoure et al. found an 8.3% prevalence of cognitive impairment in their study [26].

The significant difference in memory recall agrees with results of Mapoure et al. who also found memory recall deficits and with Quarantini et al., who observed more visual memory recall impairment in HCV patients than in HBV patients [26,27].

In our patients, altered recall memory did not correlate with hepatic

fibrosis or HCV genotype, in line with previous research [7,8,11].

Dirks et al. observed that HCV patients had worse performance than controls and HBV patients on attention and working memory tasks. Figure recognition was impaired in patients with HCV infection [28].

Cordoba et al. evaluated 120 HCV patients (40 without cirrhosis, 40 with compensated cirrhosis (without prior decompensation), and 40 with cirrhosis with previous decompensations) and found no differences on the cognitive assessment of HCV patients without cirrhosis and patients with compensated cirrhosis [12]. Abrantes et al. used very strict inclusion criteria in their study and found no differences between HCV patients and controls on any of the tests in the extensive battery of neuropsychological tests applied [13].

Of the 31 patients who had some level of memory recall deficit, only 5 (16.1%) had high grade hepatic fibrosis. However, of the 9 patients with advanced fibrosis, 5 (55.6%) had some impairment in memory recall. The possibility that the memory recall difference between the groups may have been due to MHE cannot be ruled out, where confirmation would require ammonia blood level measurements.

Minimal hepatic encephalopathy (MHE) is detected in clinically asymptomatic patients through psychometric tests and appropriate neurophysiological methods. MHE is clinically relevant as it affects quality of life, work performance, the ability to drive, as well as being a risk factor for falls and overt hepatic encephalopathy in patients with chronic liver disease [15,29]. The transition between the stages of liver disease and cognitive impairment is gradual and the exact demarcation of the onset of MHE is difficult [29]. As was shown by Giménez-Garzó et al., patients with liver cirrhosis of different etiologies that do not have MHE on the Psychometric Hepatic Encephalopathy Score, that is, patients classified as "without MHE," have some neurological alterations that are not detected by this scale, which is considered the "gold standard" for MHE [30].

Studies support the notion of an interaction between hyperammonemia and inflammation in neurological changes in MHE [31]. Hyperammonemia induces neuroinflammation, which plays an important role in neurological impairment in MHE. In addition, serum levels of proinflammatory cytokines, IL-6 and IL-18 correlate with the presence of MHE. Several proinflammatory cytokines appear to be activated in chronic HCV infection [32]. Evidence for a direct role of peripheral proinflammatory cytokines in determining impairment of cognitive function was obtained from animal models. The increase in peripheral IL-1 and IL-6 appears to correlate with increased levels of the same cytokines in the prefrontal cortex and hippocampus [32].

García-García et al. found that cirrhotic patients (both with and without MHE) had reduced hippocampal fimbria volume compared to controls, besides lower functional connectivity of the pre-subiculum and pre-cuneus bilaterally, which correlated with cognitive and memory impairment [31].

Although mild cognitive impairments observed in HCV infection are not progressive, such as in HIV-associated dementia, it has been suggested that they may result from brain immune activation, possibly as a result of HCV infection of the CNS [7].

Brain SPECT studies by Weissenborn et al. imply alterations in monoaminergic neurotransmission in the pathophysiology of HCV-associated brain dysfunction, with 50–60% of the HCV exposed patients showing significant reductions in serotonin transporter (SERT) binding in the hypothalamus and midbrain and the dopamine transporter (DAT) in the striatum [8].

In this study, 44.7% of the patients had depressive symptoms, in agreement with other reports in the literature [33,34]. Depression is considered one of the most frequent extra-hepatic manifestations of chronic HCV infection where one-third or more of those infected with HCV have depression, often undiagnosed [24]. The same proportion of depressive symptoms found in patients and controls is perhaps due to the recruiting of the control subjects from a group with similar socioeconomic status. A review of neuropsychiatric symptoms commonly associated with HCV infection by Cruz Neves et al. showed that major

depression was related to the perception of the disease, functional disability, low quality of life, severe fatigue, and to the presence of active psychiatric comorbidity [34]. These authors found that all the studies analyzed in their review systematically reported an increase in the prevalence of major depression in HCV patients (affecting 5.7–45% of patients), except for the study by Johnson et al. [35].

The pathogenesis of symptoms of neuropsychiatric disorders related to chronic HCV infection is poorly understood and it has yet to be determined whether the occurrence of depression is a risk factor or a consequence of the infection. Patients with depression may have a higher incidence of HCV infection. A large contingent of intravenous drug users are HCV infected, many of whom have clinical depression [35]. On the other hand, depression may be a reactive phenomenon to the diagnosis and concerns about health and disease evolution or may be secondary to symptoms such as fatigue and cognitive impairment [7,8]. Some authors have also hypothesized that a biological effect of the HCV infection may underlie the depression [8].

As the presence of major depression may lead to impairment in executive functions, most studies assessing cognitive impairment in patients with hepatitis C exclude individuals with depression. However, as stated by some authors, the high rates of depression reported in HCV patients may be a neuropsychiatric manifestation resulting from the direct or indirect action of the virus on the brain. Therefore, exclusion of these patients may result in selection bias, since only patients with fewer cognitive manifestations of HCV infection would be evaluated [7,8,13]. In the present study, patients with depression were not excluded from the comparison of cognitive screening results. This fact, however, did not influence results, since the proportion of patients and controls reporting depressive, anxious and hopeless symptoms was the same in both groups.

We found no significant difference in the proportion of patients with depressive symptoms among individuals who had a history of recreational drugs use compared to those who did not. A history of alcoholism or both conditions also did not seem to influence cognitive test results.

This study has several limitations. The relatively small size of the groups limits the statistical power of the study. The examiners were aware of the serological status of the participants. Participants with a history of alcohol and drug use were not excluded, although we did not find differences between those who had and had no history of alcohol abuse and illicit drugs in Beck's inventory scores and cognitive assessment.

The tests used for cognitive screening, very useful in clinical practice, lack the sensitivity of the most complete neuropsychological batteries and this may lead to an underestimation of the real burden on the cognition represented by chronic HCV infection.

The control group consisted mainly of relatives, spouses or relatives of non-HCV patients from the same institution. This fact may be positive since the participants have a similar social history, which may explain, at least in part, the lack of difference between groups in relation to the Beck Inventory scores.

A positive aspect of this study is that patients and controls were evaluated by the same neurologist and the same psychologist and added some data to the understanding of the burden of hepatitis C virus infection.

In summary, the cognitive deficits of patients with chronic hepatitis C without signs of encephalopathy, despite advanced liver fibrosis, were subtle and present only in some individuals with HCV infection. In others, the disease proves a truly asymptomatic condition. These symptoms likely stem from a complex interaction between viral and host genetic factors and external stressor events. Further studies using comprehensive neuropsychological and neuropsychiatric evaluations, focusing on memory (delayed recall), attention and depressive symptoms will lead to a better understanding of this complex interaction.

5. Conclusions

No statistical differences in total scores on the cognitive evaluation tests were found between HCV patients and control subjects. Memory recall differed significantly between the groups and was not due to depression, educational level, age or presence of comorbidities, such as history of alcoholism or drug abuse. No differences were observed between patients and controls for symptoms of depression, anxiety or hopelessness. A negative correlation was found between viral load and liver fibrosis grade and between fibrosis grade and the performance in the direct order digit test. Viral load and HCV genotypes were not associated with any other variables studied.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

References

[1] World Health Organization, Global Health Sector Strategy on Viral Hepatitis, 2016–2021: Towards Ending Viral Hepatitis. [Internet], Available at http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV2016.06-eng.pdf.

[2] P. Cacoub, C. Renou, E. Rosenthal, P. Cohen, I. Loury, V. Loustaud-Ratti, et al., Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients, The GERMIVIC. Groupe d'Etude et de Recherche En Medecine Interne et Maladies Infectieuses Sur Le Virus de l'Hepatite C. Medicine (Baltimore) 79 (2000) 47–56 (PMID: 10670409).

[3] D.V. Stefanova-Petrova, A.H. Tzvetanska, E.J. Naumova, A.P. Mihailova, E.A. Hadjiev, R.P. Dikova, et al., Chronic hepatitis C virus infection: prevalence of extrahepatic manifestations and association with cryoglobulinemia in Bulgarian patients, World J. Gastroenterol. 13 (48) (2007) 6518–6528, https://doi.org/10.3748/wjg.v13.i48.6518.

[4] C. Ferri, M. Sebastiani, D. Giuggioli, M. Colaci, P. Fallhi, A. Piluso, et al., Hepatitis C virus syndrome: a constellation of organ e non-organ specific immune disorders, B-cell non-Hodgkin's lymphoma, and cancer, World J. Hepatol. 7 (3) (2015) 327–343, https://doi.org/10.4254/wjh.v7.i3.327.

[5] L.E. Adinolfi, R. Nevola, G. Lus, L. Restivo, B. Guerrera, A. Marrone, et al., Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview, World J. Gastroenterol. 21 (2015) 2269–2280, https://doi.org/10.3748/wjg.v21.i8.2269.

[6] G.R. Foster, R.D. Goldin, H.C. Thomas, Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis, Hepatology. 27 (1998) 209–212, https://doi.org/10.1002/hep.510270132.

[7] D.M. Forton, H.C. Thomas, C.A. Murphy, J.M. Allsop, G.R. Foster, J. Main, et al., Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease, Hepatology 35 (2002) 433–439, https://doi.org/10.1053/jhep.2002.30688.

[8] K. Weissenborn, J.C. Ennen, M. Bockmeyer, B. Ahl, U. Wurter, H. Tillmann, et al., Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment, Gut 55 (2006) 1624–1630, https://doi.org/10.1136/gut.2005.080267.

[9] R. Hilsabeck, T.I. Hassanein, M. Carlson, E.A. Ziegler, Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C, J. Int. Neuropsychol. Soc. 9 (6) (2003) 847–854, https://doi.org/10.1017/S1355617703960048.

[10] M.P. McAndrews, K. Farcnik, P. Carlen, A. Damyanovich, M. Mrjonjic, S. Jones, et al., Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors, Hepatology. 41 (2005) 801–808, https://doi.org/10.1002/hep.20635.

[11] D. Lowry, B. Coughlan, O. McCarthy, J. Crowe, Investigating health-related quality of life, mood and neuropsychological test performance in homogeneous cohort of Irish female hepatitis C patients, J. Viral Hepat. 17 (2010) 352–359, https://doi.org/10.1111/j.1365-2893.2009.01188.x.

[12] J. Cordoba, M. Flavia, C. Jacas, S. Sauleda, J.I. Esteban, V. Vargas, et al., Quality of life and cognitive function in hepatitis C at different stages of liver disease, J. Hepatol. 39 (2) (2003) 231–238, https://doi.org/10.1016/S0168-8278(03)00189-2.

[13] J. Abrantes, D.S. Torres, C.E. de Mello, Patients with hepatitis C infection and

normal liver function: an evaluation of cognitive function, Postgrad. Med. J. 89 (2013) 433–439, https://doi.org/10.1136/postgradmedj-2012-131185.

[14] B. Sureka, K. Bansal, Y. Patidar, S. Rajesh, A. Mukund, A. Arora, Neurologic manifestations of chronic liver disease and liver cirrhosis, Curr. Probl. Diagn. Radiol. 44 (5) (2015) 449–461, https://doi.org/10.1067/j.cpradiol.2015.03.004.

[15] K. Weissenborn, S. Heidenreich, K. Giewekemeyer, N. Ruckert, H. Hecker, Memory function in early hepatic encephalopathy, J. Hepatol. 39 (2003) 320–325, https://doi.org/10.1016/S0168-8278(03)00295-2.

[16] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198 (PMID:1202204).

[17] S.M. Brucki, R. Nitrini, P. Caramelli, P.H. Bertolucci, I.H. Okamoto, Suggestions for utilization of the mini-mental state examination in Brazil, Arq. Neuropsiquiatr. 61 (2003) 777–781, https://doi.org/10.1590/S0004-282X2003000500014 (3-B.

[18] T. Sunderland, J.L. Hill, A.M. Lellow, B.A. Lawlor, J. Gundersheimer, P.A. Newhouse, et al., Clock drawing in Alzheimer's disease. A novel measure of dementia severity, J. Am. Geriatr. Soc. 37 (8) (1989) 725–729 2754157.

[19] K. Shulman, Clock-drawing: is it the ideal cognitive screening test? Int. J. Geriatr. Psychiatry 15 (6) (2000) 548–561 1086192.

[20] S.M. Brucki, S.M. Malheiros, I.H. Okamoto, P.H. Bertolucci, Normative data on the verbal fluency test in the animal category in our milieu, Arq. Neuropsychiatr. 55 (1) (1997) 56–61 (PMID:9332561).

[21] M.D. Lezak, D.B. Howieson, D.W. Loring, Neuropsychological Assessment, 4th ed, Oxford University Press, New York, 2004.

[22] A.T. Beck, C.H. Ward, M. Mendelsohn, J. Mock, J. Erbaugh, An inventory for measuring depression, Arch. Gen. Psychiatry 4 (1961) 561–571 (PMID:13688369).

[23] E.V. Mello, V.A. Ferreira Alves, Chronic hepatitis C: pathological anatomy. In consensus of the Brazilian Society of Infectious Diseases on the anagement and treatment of hepatitis C, Braz. J. Infect. Dis. 11 (Suppl. 1) (2007) 32–36, https://doi.org/10.1590/S1413-86702007000700001.

[24] L. Kramer, E. Bauer, G. Funk, H. Hofer, W. Jessner, P. Steindl-Munda, et al., Subclinical impairment of brain function in chronic hepatitis C infection, J. Hepatol. 37 (2002) 349–354 22798739.

[25] R.J. Fontana, L.A. Bieliauskas, C. Back-Madruga, K.L. Lindsay, Z. Kronfol, A.S. Lok, et al., Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial, J. Hepatol. 43 (4) (2005) 614–622, https://doi.org/10.1016/j.jhep.2005.04.006.

[26] N.Y. Mapoure, M.N. Budzi, S.A.F.B. Eloumou, A. Malongue, C. Okalla, H.N. Luma, Neurological manifestations in chronic hepatitis C patients receiving care in a reference hospital in sub-Saharan Africa: a cross-sectional study, PLoS One 13 (3) (2018) e0192406, , https://doi.org/10.1371/journal.pone.0192406.

[27] L.C. Quarantini, A. Miranda-Scippa, S. Batista-Neves, V.B. Powell, N. Abreu, K.C. Abreu, et al., A neuropsychological study comparing patients infected with HCV and HBV without psychiatric comorbidities, J. Med. Virol. 81 (2009) 1184–1188, https://doi.org/10.1002/jmv.21508.

[28] M. Dirks, K. Haag, H. Pflugrad, A.B. Tryc, R. Schuppner, H. Wedemeyer, et al., Neuropsychiatric symptoms in hepatitis C patients resemble those of patients with autoimmune liver disease but are different from those in hepatitis B patients, J. Viral Hepat. (2018), https://doi.org/10.1111/jvh.12979 (Epub ahead of print).

[29] L. Ridola, V. Cardinale, O. Riggio, The burden of minimal hepatic encephalopathy: from diagnosis to therapeutic strategies, Ann. Gastroenterol. 31 (2) (2018) 151–164, https://doi.org/10.20524/aog.2018.0232.

[30] C. Giménez-Garzó, J.J. Garcéz, A. Urios, A. Mangas-Losada, R. García-García, O. Gonzáles-López, et al., The PHES battery does not detect all cirrhotic patientes with early neurological deficits, PLoS One 2 (2) (2017) e0171211, , https://doi.org/10.1371/journal.pone.0171211 (eCollection 2017).

[31] R. García-García, A.J. Cruz-Gómez, A. Urios, A. Mangas-Losada, C. Forn, D. Escudero-García, et al., Learning and memory impairments in patients with minimal hepatic encephalopathy are associated with structural and functional connectivity alterations in hippocampus, Sci. Rep. 8 (1) (2018) 9664, https://doi.org/10.1038/s41598-018-27978-x.

[32] R. Zampino, A. Marrone, L. Restivo, B. Guerrera, A. Sellitto, L. Rinaldi, et al., Chronic HCV infection and inflammation: clinical impact on hepatic and extra-hepatic manifestations, World J. Hepatol. 5 (2013) 528–540, https://doi.org/10.4254/wjh.v5.i10.528.

[33] J. Golden, A.M. O'Dwyer, R.M. Conroy, Depression and anxiety in patients with hepatitis C: prevalence, detection rates and risk factors, Gen. Hosp. Psychiatry 27 (2005) 431–438, https://doi.org/10.1016/j.genhosppsych.2005.06.006.

[34] A. Cruz Neves, C. Dickens, M. Xavier, Comorbidity between hepatitis C and depression. Epidemiological and etiopathogenic aspects, Acta Medica Port. 19 (2006) 21–28.

[35] M.E. Johnson, D.G. Fisher, A. Fenaughty, S.A. Theno, Hepatitis C virus and depression in drug users, Am. J. Gastroenterol. 93 (1998) 785–789, https://doi.org/10.1111/j.1572-0241.1998.225_a.x.