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Original article

Psychiatric and functional neuroimaging abnormalities in chronic hepatitis C virus patients: Is vasculitis a contributing factor?

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ABSTRACT

Background and study aims: Central nervous system (CNS) involvement in hepatitis C virus (HCV) infection has different facets such as anxiety, depression, cognitive impairment and vasculitis. We were interested in detecting subclinical CNS involvement in chronic HCV infected subjects with and without systemic vasculitis.

Patients and methods: Nineteen patients (15 females and 4 males) with chronic HCV infection (mean age 46.5 ± 7 and mean duration since diagnosis of HCV infection 4.7 ± 4 years, including 6 (32%) Child-Pugh class A cirrhotic patients) and 30 age, sex and education matched healthy control subjects were studied. Thirteen patients had associated vasculitis. Patients and control subjects were assessed using the block design and comprehension subtests of Wechsler Bellevue Adult Intelligence Scale, Wechsler Memory scale (WMS), Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI). Brain HMPAO Single Photon Emission Computed Tomography (SPECT) was performed for HCV patients.

Results: Patients with HCV had lower scores on the block design test compared to control subjects (8.37 ± 1.89 versus 10.37 ± 1.47, $p < 0.001$), lower total WMS scores (43.15 ± 10.49 versus 60.27 ± 8.08, $p < 0.001$) and higher anxiety and depression scores (16.94 ± 10.46 and 37.17 ± 10.38 versus 10.3 ± 4.67 and 28.9 ± 5.99, $p = 0.004$ and 0.001, respectively). Total WMS were lower in HCV patients with vasculitis compared to those without vasculitis (39.14 ± 9.3 versus 51.17 ± 8.3, $p = 0.019$) while the block design and comprehension tests, BAI and BDI were not significantly different between both groups. The block design and comprehension tests, WMS, BAI and BDI were not significantly different between cirrhotic and non-cirrhotic patients. Seven patients had different patterns of cerebral hypoperfusion on SPECT, and all of them had associated vasculitis. Abnormal SPECT was associated with lower total WMS scores (35.87 ± 10.8 versus 46.79 ± 8.6 in those with normal SPECT, $p = 0.049$).

Conclusions: Vasculitis may contribute to the development of neuropsychiatric involvement in HCV patients.

Introduction

Hepatitis C virus (HCV) is a hepatotropic and lymphotropic virus that is associated with a wide variety of extrahepatic manifestations, many of which are rheumatic or autoimmune in nature. Central nervous system (CNS) involvement in chronic HCV infection may present different facets, such as fatigue, depression, cognitive impairment and vasculitis [1]. Cryoglobulinaemic vasculitis is the most distinctive extrahepatic manifestation related to chronic HCV infection, involving small and medium sized blood vessels [2], however, systemic vasculitis associated with HCV infection in the absence of detectable cryoglobulins may occur [3]. The peripheral nervous system is frequently involved in HCV-associated mixed cryoglobulinaemic vasculitis while central nervous system affection is rare [1,4].

There has been growing evidence that alterations in cerebral function in patients with chronic HCV infection may appear long before the development of severe liver fibrosis/cirrhosis, however,

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these alterations cannot be ascribed to hepatic encephalopathy [5]. Their aetiology is unclear but it has been hypothesized that it is related to a direct effect of HCV on the brain [6] or the neurotoxic effect of HCV-related cerebral/systemic inflammation [7]. This study was performed to detect subclinical central nervous system involvement in chronic HCV infected subjects with or without vasculitis using psychometric assessment and single photon emission computed tomography (SPECT) imaging of the brain.

Patients and methods

This is a cross-sectional case control descriptive study. It comprised nineteen patients (15 females and 4 males) with chronic HCV infection with or without vasculitis, with ages ranging from 28 to 65 years. They were recruited from the Rheumatology and Internal Medicine Departments at Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University during the period from November 2012 to November 2014. Thirty age, sex and education matched healthy subjects from the employees of Cairo University Hospitals who volunteered to participate in the study were included as a control group. All patients and control subjects gave informed written consent to participate in the study which conforms to the provisions of the World Medical Association's Declaration of Helsinki. Vasculitis was diagnosed according to the validated classification criteria for cryoglobulinaemic vasculitis which are also useful for classification of patients who have undetectable cryoglobulins on initial laboratory testing [3]. Exclusion criteria included patients with concomitant neurological or psychiatric diseases, substance abuse, cirrhotic patients with Child-Pugh score [8] >B, those with positive tests for hepatitis B and human immunodeficiency viruses, interferon therapy or other medications that might impair cerebral function. The estimated disease duration was calculated from the date of HCV diagnosis where chronic HCV infection was confirmed by quantitative polymerase chain reaction (PCR). Laboratory assessment for HCV patients included sedimentation rate, complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, bilirubin, international normalized ratio, creatinine, cryoglobulins, complement components C3 and C4 and urine analysis. Cirrhotic patients (documented either by liver biopsy or Fibroscan [9]) were classified according to the Child-Pugh score using laboratory and ultrasonographic data [8]. Psychometric assessment was done for patients and controls. All patients were subjected to single photon emission computed tomography (SPECT) imaging of the brain.

Psychometric assessment

The comprehension subtest from the verbal domain of the Wechsler Bellevue Adult Intelligence scale (WAIS) was applied to assess the verbal reasoning (logical thinking, production of language, acquired knowledge and rote memorization of facts) while the block design subtest of the WAIS was used to assess perceptual reasoning (spatial visualization and motor skills) [10]. Arabic versions of the Beck depression inventory II (BDI) [11] and Beck anxiety inventory (BAI) [12] were used to assess the severity of depression and anxiety. Memory performance was assessed to test different memory functions including auditory, visual, visual working, immediate and delayed memory using the Wechsler Memory Scale – Revised short form (WMS) which comprises a series of brief subtests each measuring a different facet of memory. It includes subtests for information, orientation, mental control, logical memory, digit span, associate learning and visual reproduction [13].

Brain HMPAO-SPECT

All HCV patients underwent brain SPECT using Tc-99 m HMPAO to detect CNS involvement by depicting cerebral blood flow disturbances. A dual head gamma camera fitted with a low-energy high-resolution collimator was used (Philips Axis Gantry Odyssey Linux, Kernel software V7.0–1.7 12/14/01, the Netherlands). Acquisition began 30–60 min after the IV injection of 740 MBq Tc-99 m HMPAO while the patient was sitting, eyes open, in a quiet dimly lit room. Image reconstruction was performed through a closed computer program into transaxial, coronal, and sagittal cuts.

Statistical methods

All statistical methods were performed using SPSS-14 program for windows. Pearson Chi-square test or Fisher's exact test was used to compare frequencies between groups. Mann Whitney test was used to compare continuous variables between 2 groups. Spearman's correlation coefficient was used for correlations. P values ≤ 0.05 were considered statistically significant.

Results

Clinical and laboratory data of HCV patients

The mean age of the patients was 46.5 ± 7.9 years (range: 28–56 years) and 15 (79%) were females. The mean time since diagnosis of HCV infection was 4.7 years (±4 years). Liver cirrhosis was present in 6/19 (32%) patients (All were Child A classification). All patients had positive viremia (mean viral load $0.54 \times 106 \pm 6.8 \times 106$ copies/ml). They had a mean ESR of 44.3 ± 27.81 mm/h, mean ALT level of 50.07 ± 48.85 IU/l and mean AST level of 50.07 ± 39.2 IU/l. Clinical manifestations of vasculitis were seen 13/19 (68%) patients; nine patients had arthralgia/arthritis; cutaneous manifestations were found in ten patients in the form of purpura in six patients, toe gangrene in two patients and livedo reticularis, Raynaud's phenomenon and papular itchy rash in one patient each; one patient had renal involvement in the form of minimal change glomerulonephritis; neurological manifestations were in the form of sensory painful peripheral neuropathy in three and mononeuritis multiplex in four patients. Serum cryoglobulins were detected in 5/13 (38.46%) vasculitis patients. Four vasculitis patients were cirrhotic.

Psychometric assessment of HCV patients and control subjects

Psychometric assessment was performed to HCV patients and thirty healthy controls (mean age 43.8 ± 8.6 including 22 females). No statistically significant differences were found between patients and controls regarding age, gender and level of education ($p = 0.28$ and 0.74, respectively).

Concerning the level of education, among the HCV patients, 11(57.9%) were illiterate, 3(15.7%) could read and write and 5(26.3%) had a middle-level education while among the control subjects, 18(60%) were illiterate, 5(16.7%) could read and write and 7(23.3%) had a middle level education; these differences were not statistically significant ($p = 0.94$). Comparison of psychometric tests between HCV patients and the control group revealed significantly lower scores on the block design subtest of the WAIS and significantly higher anxiety and depression scores in HCV patients ($p < 0.001$, $p = 0.004$ and 0.001, respectively). All items of the WMS were significantly lower in HCV patients ($p < 0.05$), Table 1.

Among the studied patients, 11/19 HCV patients were found to have significant abnormality in one or more subscales of the WMS according to the proposed normal values. The total WMS was

Table 1
Psychometric tests in HCV patients and healthy controls.

Neuro-psychological test	Subjects		p
	HCV N = 19	Control N = 30	
WAIS			
Comprehension	9.42 ± 2.99	10 ± 1.3	0.33
Block design	8.37 ± 1.89	10.37 ± 1.47	<0.001*
WMS			
General information	3.94 ± 1.47	5.5 ± 0.78	0.001*
Orientation	3.83 ± 1.04	4.5 ± 0.51	0.005*
Mental control	3.83 ± 1.54	5.13 ± 0.9	0.001*
Logical memory	7.39 ± 2.59	12.23 ± 3	<0.001*
Digit span	7.5 ± 1.15	9.7 ± 1.58	<0.001*
Associate learning	7.81 ± 3.91	12.63 ± 3.15	<0.001*
Visual reproduction	7.83 ± 2.2	10.57 ± 1.17	<0.001*
Total	43.15 ± 10.49	60.27 ± 8.08	<0.001*
BAI	16.94 ± 10.46	10.3 ± 4.67	0.004*
BDI	37.17 ± 10.38	28.9 ± 5.99	0.001*

WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory. Mann Whitney test was used for comparisons; *, statistically significant.

significantly correlated with the comprehension and block design subtests of the WAIS (p = 0.025 and 0.035, respectively), but not correlated to either anxiety or depression scores (Table 2).

No statistically significant differences were found between cirrhotic and non-cirrhotic patients regarding WAIS comprehension (11 ± 5.7 versus 8.4 ± 1.8, p = 0.7) and WAIS block design test (8.3 ± 1.3 versus 8 ± 2.5, p = 0.69), BAI (17.5 ± 8.6 versus 17.8 ± 11, p = 0.73), BDI (34.8 ± 9.4 versus 35.9 ± 10.6, p = 0.73) or in the total WMS (37.4 ± 7.4 versus 40 ± 10.4, p = 0.396).

Among all patients, no significant correlations were found between total WMS and either of the following: disease duration, viral load, ALT or AST levels or ESR (r = 0.37, −0.006, −0.32, −0.18, r = −0.5; p = 0.24, 0.99, 0.31, 0.57 and 0.075, respectively).

Psychometric assessment of HCV patients with vasculitis

Comparing HCV patients with and without vasculitis, the items of block design and comprehension of the WAIS, BAI, and BDI showed no statistically significant differences, however, among patients with vasculitis, the digit span (7.17 ± 1.3 vs. 8.17 ± 0.4) and the associate learning subscales of the WMS (6.21 ± 2.5 vs. 11 ± 4.4) were significantly lower (p = 0.038 and 0.031, respectively). There were no statistically significant differences between other subtests of the WMS between HCV patients with or without vasculitis, while the total WMS was significantly lower among those with vasculitis (39.14 ± 9.3 vs. 51.17 ± 8.3; p = 0.019). Correlations between individual subscales and the total WMS scores with selected disease-related parameters are shown in Table 3. Significant positive correlations were found between general information and the disease duration (p = 0.042), mental control and the viral load (p = 0.016) and between the digit span and ESR (p = 0.014). Notably, there were no significant correlations between any of the WMS subtests or the total WMS and the ALT or AST levels. Furthermore, none of the WMS subtests or the total WMS were significantly different between cirrhotic and non-cirrhotic vasculitis patients (Table 4). Also, no statistically significant differences were found in the total WMS scores between those positive or negative for cryoglobulins (p = 0.57).

Neuro-imaging using HMPAO-SPECT

Abnormalities were found in 7/13 patients with vasculitis while none of the HCV patients without vasculitis had an abnormal SPECT (p = 0.044). Diffuse pattern of brain hypo-perfusion with symmetrical affection of both hemispheres was detected in three patients while one patient showed predilection of the right side (Fig. 1). On the other hand, symmetrical bilateral parietal zone affection was found in two patients while one patient had left posterior parietal hypo-perfusion.

When psychometric tests were compared between patients with abnormal SPECT (n = 7) and those with normal findings (n = 12), no statistically significant differences were found in the comprehension and block design tests of the WAIS, Beck depression or anxiety scores. Patients with abnormal SPECT had significantly lower digit span (6.5 ± 1.4 versus 8 ± 0.6, p = 0.006), associate learning (4.8 ± 2.5 versus 9.29 ± 3.7, p = 0.017), and total WMS scores (35.87 ± 10.8 versus 46.79 ± 8.6, p = 0.049) as compared to patients with normal SPECT (Fig. 2).

Table 2
Correlation between total WMS score and neuro-psychological tests.

Neuro-psychological test	WMS	
	r	p
WAIS		
Comprehension	0.53	0.025*
Block design	0.5	0.035*
BAI	−0.03	0.92
BDI	0.22	0.38

WMS, Wechsler Memory Score; WAIS, Wechsler Adult Intelligence Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory. Spearman's correlation coefficient; *, statistically significant.

Discussion

In the present study, significant cognitive affection was found in 11/19 HCV patients (58%) without overt CNS involvement, more evident in those with vasculitis. Cerebral hypo-perfusion on SPECT imaging was found in 7/19 (37%) patients, and all of these had associated vasculitis, suggesting a primary blood flow deficit or a local metabolic disturbance [14]. Abnormal imaging on SPECT was significantly associated with lower scores on the WMS suggesting a role of intracerebral inflammation in the development of cognitive impairment.

Nearly one-third of HCV-positive patients can be diagnosed with different cognitive disorders, generally of mild degree [15]. Although the literature shows a clear evidence of cognitive dysfunction in HCV patients [16], some studies found no association between cognitive function and chronic HCV infection [17,18]. HCV patients in the present study had significantly lower scores on the block design test (reflecting a deficit in spatial visualization and motor skills) [10] and all items of the WMS denoting impairment in auditory, working, visual working, immediate and delayed memory compared to the control group [13]. In this respect, other investigators found deficits in concentration and speed of memory processes [19], attention [20], verbal learning efficiency [21], verbal recall functions [22], processing speed and verbal fluency [23].

Higher levels of anxiety and depression were also found in HCV patients compared to healthy controls in the present study, and these were not correlated to the WMS scores, which is in agreement with other studies [19–21,24] while Fontana et al. [22] found that depression was a predictor of cognitive impairment in HCV patients.

Using proton magnetic resonance spectroscopy, several investigators were able to demonstrate abnormalities in cerebral neurometabolites such as an increase in the choline/creatine ratio in the basal ganglia and white matter [19] and lower levels of N-acetylaspartate in bilateral parietal white matter and elevations in myo-inositol in bilateral frontal white matter in HCV patients [23]. In both studies, these abnormalities were associated with cognitive impairment.

Table 3
Correlation between WMS subscales and selected variables among patients with vasculitis (n = 13).

Wechsler memory scale		ALT	AST	Viral Load	Disease duration	ESR
General information	r_s	−0.504	−0.242	−0.043	0.594	0.295
	p value	0.095	0.449	0.905	0.042*	0.352
Orientation	r_s	−0.343	−0.162	−0.208	0.48	−0.036
	p value	0.275	0.616	0.565	0.114	0.911
Mental control	r_s	0.311	0.207	0.731	0.341	−0.004
	p value	0.326	0.518	0.016*	0.278	0.991
Logical memory	r_s	−0.161	0.062	−0.342	0.494	0.183
	p value	0.616	0.847	0.334	0.103	0.57
Digit span	r_s	−0.432	−0.391	0.076	−0.034	0.687
	p value	0.161	0.208	0.835	0.918	0.014*
Associate learning	r_s	0.106	0.055	−0.006	0.172	0.358
	p value	0.744	0.866	0.987	0.594	0.253
Visual reproduction	r_s	−0.374	−0.238	0.228	0.25	0.431
	p value	0.231	0.456	0.527	0.433	0.161
Total	r_s	−0.323	−0.182	−0.006	0.367	0.531
	p value	0.306	0.57	0.987	0.241	0.075

rs: Spearman's correlation coefficient; *, statistically significant.

Table 4
WMS subscales, comparison between cirrhotic and non-cirrhotic patients with vasculitis.

Neuro-psychological test	Group of patients [mean (±SD)]		p value
	Cirrhotic n = 4	Non-cirrhotic n = 9	
Wechsler Memory Scale			
General information	3.25 (1.26)	3.63 (14.1)	0.662
Orientation	3.75 (1)	3.5 (1.2)	0.725
Mental control	4.25 (0.5)	3.25 (1.98)	0.387
Logical memory	6.5 (1.92)	6.63 (2.33)	1
Digit span	7 (0.82)	7.25 (1.49)	0.419
Associate learning	5.63 (1.65)	6.5 (2.92)	0.394
Visual reproduction	7 (2.45)	8.13 (2.53)	0.544
Total	37.43 (7.42)	40 (10.44)	0.396

Using diffusion tensor imaging, microstructural abnormalities were demonstrated in the corpus striatum, external capsule, and fronto-occipital fasciculus in HCV patients compared to controls [23,25] and were associated with poor cognitive performance [23]. Kramer et al. [26] demonstrated subclinical cognitive dysfunction by P300 event-related potentials, a sensitive electrophysiologic test of cognitive processing in a subset of non-cirrhotic HCV patients. A possible mechanism for cognitive decline in HCV patients could be the alterations in serotonergic and dopaminergic neurotransmission in the hypothalamus, midbrain and striatum as studied by SPECT [27]. The previous studies thereby provided evidence of a biological link between cognitive dysfunction and chronic HCV infection, i.e. that the cognitive impairments in HCV infected subjects are caused by the virus itself, not due to confounders such as psychiatric disorders, substance abuse, interferon therapy or liver cirrhosis [16,28].

In the present study, diffuse hypo-perfusion of both cerebral hemispheres or focal hypoperfusion of the parietal lobes were detected on brain SPECT in 7/19 (37%) of HCV patients, which could be explained by the presence of subclinical cerebral vasculitis. None of the patients without systemic vasculitis had abnormalities on SPECT. In this respect, using perfusion- weighted MR imaging, Bladowska et al. [25] demonstrated significantly lower relative cerebral blood volume values (compared to the cerebellum) within the frontal and temporo-parietal cortices and increased relative cerebral blood in the basal ganglia among HCV-positive patients as compared to control subjects.

There is controversy whether cognitive affection in HCV is related to the degree of hepatic involvement. In the current study, no statistically significant differences were found in total WMS between cirrhotic and non-cirrhotic patients and no correlations were found between WMS and ALT, AST levels or viral load. In agreement with our results, Cordoba et al. [17] showed that neuropsychological tests were unimpaired in HCV patients with chronic hepatitis or compensated liver cirrhosis being impaired only in those with advanced cirrhosis, and other investigators found no correlation between the cognitive test scores and the degree of liver fibrosis [21,22,26]. On the contrary, Hilsabeck et al. [25] found an association between cognitive impairment and greater fibrosis stage. In concordance with our results, several studies found no correlation between cognitive function scores and ALT levels [19,21] or viral load [21,26].

Apart from case reports, only few studies have specifically evaluated the CNS involvement in HCV patients with systemic vasculitis [29,30]. Casato et al. [29] found that HCV patients with cryoglobulinemic vasculitis had a higher mean number of periventricular and total white matter high intensity signals on MR brain images and more frequent abnormalities on cognitive testing than

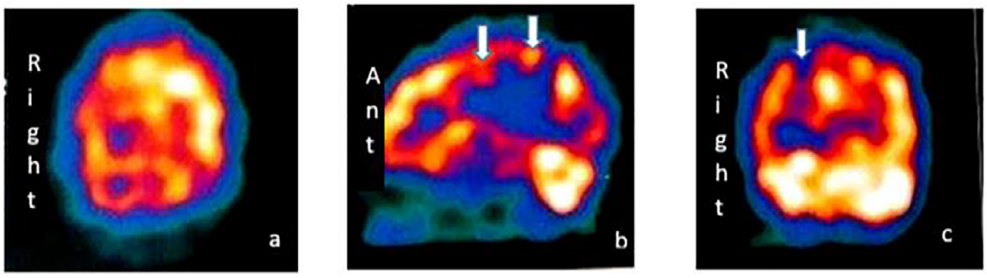

Fig. 1. The HMPAO- SPECT images (a, transaxial; b, sagittal and c, coronal cuts) show multiple brain hypo-perfusion areas involving the fronto-parietal and parieto-occipital regions, predominantly affecting the right side. According to General Electric color strip code, the color may vary from deep yellow (denoting normal blood flow) to black (denoting necrosis and absence of blood flow).

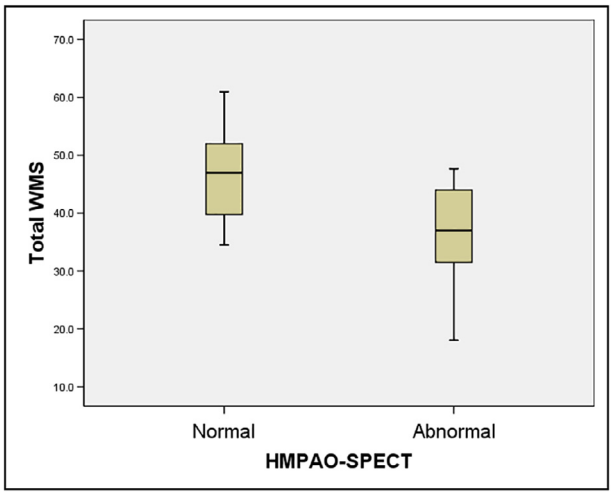

Fig. 2. Total Wechsler memory Score (WMS) score in HCV patients according to the result of HMPAO-SPECT scan.

HCV controls without vasculitis. Moreover, the cryoglobulin level was positively correlated with the number of impaired cognitive functions. The authors suggested that a specific cerebral small vessel vasculitis possibly contributes to the observed abnormalities. Cappellari et al. [30], in an uncontrolled study, described cognitive abnormalities in 22%, abnormal evoked potentials in 83% and focal or diffuse atrophy on MR images in 83% of their patients with cryoglobulinemic vasculitis.

In line with the previous studies, in the present study, HCV patients with vasculitis were found to have lower performance on the digit span (denoting a deficit in auditory short-term memory) and the associate learning subtest (a measure of rote verbal learning) as well as the total WMS [13] compared to HCV patients without vasculitis, and the abnormalities on SPECT were only found among those with vasculitis.

Significant correlations were found between the general information subscale and disease duration ($p = 0.042$), mental control and viral load ($p = 0.016$), and between the digit span and ESR ($p = 0.014$), while no association was found between the presence of cryoglobulins and the total WMS. Notably, none of the subtests of the WMS were correlated with the ALT or AST levels. Also, there was no association between any of the subtests of the WMS and liver cirrhosis among vasculitis patients.

Our study has limitations, such as the small number of studied patients and not performing SPECT for the control group. This is mainly because of the high cost of SPECT imaging which prevented us from inclusion of more subjects.

To conclude, subclinical neurological involvement is frequent in HCV patients especially in those with vasculitis. Further studies with a larger number of patients are needed to confirm our results.

Conflicts of interest

The authors have no conflicts of interest.

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