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## Original article

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

Hania S. Zayed<sup>a,\*</sup>, Amr Amin<sup>b,1</sup>, Samy Alsirafy<sup>b</sup>, Nahla D. Elsayed<sup>b</sup>, Soheir Abo Elfadl<sup>c</sup>, Mohamed Nasreldin<sup>d</sup>, Dalia Enaba<sup>d</sup>, Zeinab Nawito<sup>a</sup><sup>a</sup> Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University, Cairo, Egypt<sup>b</sup> Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt<sup>c</sup> Internal Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt<sup>d</sup> Psychiatry Department, Faculty of Medicine, Cairo University, Cairo, Egypt

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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  $46.5 \pm 7$  and mean duration since diagnosis of HCV infection  $4.7 \pm 4$  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 ( $8.37 \pm 1.89$  versus  $10.37 \pm 1.47$ ,  $p < 0.001$ ), lower total WMS scores ( $43.15 \pm 10.49$  versus  $60.27 \pm 8.08$ ,  $p < 0.001$ ) and higher anxiety and depression scores ( $16.94 \pm 10.46$  and  $37.17 \pm 10.38$  versus  $10.3 \pm 4.67$  and  $28.9 \pm 5.99$ ,  $p = 0.004$  and  $0.001$ , respectively). Total WMS were lower in HCV patients with vasculitis compared to those without vasculitis ( $39.14 \pm 9.3$  versus  $51.17 \pm 8.3$ ,  $p = 0.019$ ) 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 ( $35.87 \pm 10.8$  versus  $46.79 \pm 8.6$  in those with normal SPECT,  $p = 0.049$ ).

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

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## 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,

\* Corresponding author.

E-mail address: [hania.zayed@kasralainy.edu.eg](mailto:hania.zayed@kasralainy.edu.eg) (H.S. Zayed).<sup>1</sup> In memoriam (1967–2014).<https://doi.org/10.1016/j.ajg.2018.06.003>

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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  $\leq 0.05$  were considered statistically significant.

## Results

### Clinical and laboratory data of HCV patients

The mean age of the patients was  $46.5 \pm 7.9$  years (range: 28–56 years) and 15 (79%) were females. The mean time since diagnosis of HCV infection was 4.7 years ( $\pm 4$  years). Liver cirrhosis was present in 6/19 (32%) patients (All were Child A classification). All patients had positive viremia (mean viral load  $0.54 \times 10^6 \pm 6.8 \times 10^6$  copies/ml). They had a mean ESR of  $44.3 \pm 27.81$  mm/h, mean ALT level of  $50.07 \pm 48.85$  IU/l and mean AST level of  $50.07 \pm 39.2$  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  $43.8 \pm 8.6$  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

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