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Assessment of Executive Functions in Chronic Hepatitis C Virus Infected Patients

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Abstract

Background: Chronic infection with HCV is one of the most important causes of chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma (HCC). It is well established that advanced forms of the disease are accompanied by overt and global cognitive deficits (hepatic encephalopathy) but now there is a growing evidence that the alterations in cerebral function in patients with chronic HCV infection may appear long before the development of severe liver cirrhosis, it has been hypothesized that it is related to a direct effect of HCV on the brain; or the neurotoxic effect of HCV-related systemic inflammation.

Aim: The purpose of the study was to assess the possible existence of executive dysfunction in chronic HCV infected patients without cirrhosis. **Study design:** case control study. **Participants**: 100 elderly patients aged 60 years and above, 50 patients are HCV positive (cases) and 50 patients are HCV negative (controls) both groups have no liver cirrhosis.

Methods: All participants were subjected to the following: Diagnosis of HCV by detection of HCV ab using ELISA technique, non invasive assessment of liver cirrhosis using abdominal ultrasound, and evaluation of executive functions using 5 neuropsychological tests (block design, digit span backwards, animal verbal fluency, clock drawing, and EXIT 25).

Results: The study showed that there is a significant difference between cases and controls regarding Exit 25 and Digit span backwards tests scores indicating affection of the phonological loop component of working memory among HCV positive patients.

Conclusion: Executive functions are affected in patients with chronic HCV infection without liver cirrhosis.

Key words: executive functions, HCV, no cirrhosis

Introduction

The World Health Organization (WHO) estimates 170 million individuals worldwide are infected with hepatitis C virus (HCV). Egypt had the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy. This led to a mean prevalence of HCV antibodies in persons in Egypt of 22 % (1).

It is well established that advanced forms of the disease are accompanied by overt and global cognitive deficits (hepatic encephalopathy) (2). Recently researchers and clinicians have become increasingly aware of a group of HCV patients with mild liver disease that present with a less-overt pattern of neuropsychological impairment (3).

Executive function is a set of high-level abilities that control and regulate more basic abilities like attention, memory and motor skills, they include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations (4). So, executive dysfunction can negatively influence patient quality of life (QOL) (5).

So, the purpose of this study is to investigate the possible existence of alterations in the executive functions of HCV patients without liver cirrhosis.

Subjects and Methods:

Study Design: Case control study.

Participants: 100 elderly patients aged 60 years and above, 50 patients are HCV positive (cases) and 50 patients are HCV negative (controls) both groups have no liver cirrhosis.

Participants were recruited from patient admitted to geriatric department, internal medicine department and outpatient clinics in Ain Shams University Hospital. All participants provided informed written consent before participating in the study.

Exclusion Criteria: The exclusion criteria included those who refused to participate, patients with liver cirrhosis, HBV or HIV infection, clinical signs of liver cell failure, patients receiving antiviral therapy, patients

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with dementia, delirium or depression and patients with other comorbidities affecting executive functions (e.g. Diabetes mellitus, cerebrovascular stroke, chronic kidney disease).

Methodology: All participants were subjected to the following:

a- Comprehensive geriatric assessment was done. This including full medical history, physical examination, and mini mental status examination test (MMSE), which is a brief 30-point questionnaire screening test for dementia. Normal score is ≥26 (6) and it was done in order to exclude dementia. Also, geriatric depression scale (GDS-15) was performed to exclude cases of depression. Normal GDS score is <5 (7). Activities of daily living scale (ADL) and instrumental activities of daily living scale (IADL) were determined.

b- Non-invasive assessment of liver cirrhosis was done by abdominal ultrasound to exclude liver cirrhosis as abdominal ultrasonography is a specific, reliable, non-invasive, fast, and cost-effective test that should be used as a first-line radiographic study for diagnosing cirrhosis (8).

c- Diagnosis of HCV infection: by detection of HCV antibodies using ELISA.

d- Assessment of executive functions: Was done by using 5 neuropsychological tests administrated to each participant individually, these tests were:

1. Block design test: It requires patients to take blocks that have all white sides, all red sides, and red and white sides and arrange them to make specific design drawn in a group of coloured cards. The designs progress in difficulty from simple four-block designs to more complex, nine-block designs. The task is discontinued once two trials of block-card matching are incorrectly done. Each item is scored for accuracy and for speed as well. Scores range from 0 to 42, the raw scores is then converted into standard scores. Normal scores range from 2 to 20, with higher scores indicating better performance (9).

2. Digit span backward test: Digit span-backward requires patients to repeat a series of numbers, ranging in length from two to eight digits, in reverse sequence immediately after they are read aloud by the examiner. The task is discontinued once two trials of the series of the same length are incorrectly repeated. Normal score is ≥4 (9).

3. Animal verbal fluency test: Subjects have to enumerate as many animals (four legged) as possible within one minute. Clinically, a score below 12 on the AVF is nearly always abnormal (10).

4. Clock drawing test: Patients are given a pre-drawn circle and asked to draw numbers on it look like a clock. They are then asked to draw the hands of the clock to read (10 past 11). The score is determined from the number of digits in each quadrant (0–3 = normal score and 4–7 = abnormal score) (11).

5. Exit 25 test: The exit is a 25-item interview that takes 15–20 minutes. Each item is scored from 0 (intact) to 2 (specific incorrect response or failure to perform a task). The total score is from 0 to 50, a higher score indicating executive cognitive dysfunction. A cutoff score of 15 or greater indicates executive dysfunction (12).

Statistical Analysis:

Analysis of data was performed by using the 16th version of Statistical Package for Social Science (SPSS).

Description of all data in the form of mean (M) and standard deviation (SD) for all quantitative variables was done. Frequency and percentage was done for all qualitative variables.

Comparison between quantitative variables was done using t-test to compare two groups and ANOVA (analysis of variance) to compare more than two groups. Post Hoc test was done to detect the least significant difference.

Comparison of qualitative variables was done using the Chi-square test.

Correlation coefficient also was used to find linear relation between different variables using r-test or Sperman correlation co-efficient.

Significant level measured according to P value (probability), P> 0.05 is insignificant, P<0.05 is significant, and p<0.01 is highly significant.

Results:

In this study, 50 patients have HCV infection (cases) and 50 patients are healthy controls.

The age of cases and controls ranged from 60 to 78 years and the mean age were 65.08±4.06 and 65.60±4.95 respectively. All participants were educated.

There was no significant difference between cases and controls except in the scores of Digit span backward test and Exit 25.

Discussion:

The current study has provided evidence of the existence of executive dysfunction in patients with chronic infection caused by the hepatitis C virus. These alterations occur in HCV subjects without cirrhosis.

These results showed the existence of possible direct action of HCV on the central nervous system.

These observations are in agreement with the results obtained by Weissenborn and colleagues (3), who compared neuropsychological performance in 30 PCR-positive HCV-infected patients with normal liver function, the authors found a significant deficit in attention and higher executive function in patients compared to controls.

The results of this study also agreed with the results of the study performed by Peixoto et al. (13) who conducted a case control study involved 20 patients with HCV and 20 control subjects. The executive functions were assessed by the administration of the two test batteries related to frontal lobe functioning: the Behavioral Assessment of the Dysexecutive Syndrome and the Wisconsin Card Sorting Test.

Cognitive flexibility refers to simultaneously considering multiple aspects of thought at once, whether they are two aspects of a specific object, or many aspects of a complex situation (14).

In the current study cognitive flexibility was assessed using animal verbal fluency test and it was found that there is no statistically significant difference between HCV positive patients and healthy controls. This result agreed with the results obtained by McAndrew et al. (15) who performed a study involved 37 HCV positive patients without liver cirrhosis, their cognitive flexibility was assessed using stroop interference test and the results were compared with 46 healthy controls. The results reveal intact cognitive flexibility among HCV positive patients.

Working memory refers to the brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning. It requires the simultaneous storage and processing of information (16).

It can be divided into the following three subcomponents: (i) the central executive, which is assumed to be an attentional-controlling system, (ii) the visuospatial part, which manipulates visual images and (iii) the phonological loop, which stores and repeats speech-based information (17).

In this study the visuospatial component of working memory was assessed by block design test (18) and clock drawing test (19), while the phonological loop component was assessed by the EXIT 25 test (12) and digit span backwards (17).

The results show a significant difference between HCV positive patients and healthy controls in the scores of exit 25 and Digit span backward test indicating presence of impairment in the phonological loop component of working memory but there was no significant difference between HCV positive patients and healthy controls in the scores of block Design test and clock drawing test indicating that HCV positive patients have no impairment in the visuospatial component of working memory.

This also agreed with the study performed by Hilsabeck et al. (20) to examine cognitive functioning. The study involved 66 patients with chronic hepatitis C with mean age 45.98 years, visuospatial and visuoconstructional abilities were assessed using Rey Complex Figure Test (modified version).

The results of this study revealed that basic visuospatial and visuoconstructional abilities are relatively unaffected in patients with chronic hepatitis c who didn't develop cirrhosis.

Conclusion:

The study showed that Chronic HCV infection is accompanied by impaired executive functions even in the absence of liver cirrhosis suggesting direct action of the hepatitis C virus on the frontal lobe.

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Table (1): Comparison between the case and control group as regard the executive functions tests score:

Test	Cases		Control		Chi-square	
	Normal(N%)	Abnormal(N%)	Normal(N%)	Abnormal (N%)	X2	P-value
Block Design	23(50%)	27(50%)	23(50%)	27(50%)	0.000	1.000
Digit span backward	8(30.8%)	42(56.8%)	18(69.2%)	32(43.2%)	5.198	0.023
Animal verbal fluency	12(48.0%)	38(50.7%)	13(52.0%)	37(49.3%)	0.053	0.817
Clock Drawing test	13(37.1%)	37(56.9%)	22(62.9%)	28(43.1%)	3.560	0.059
EXIT 25	33(39.8%)	17(100%)	50(60.2%)	0(0%)	20.482	0.000