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# A Neuropsychological Study Comparing Patients Infected With HCV and HBV Without Psychiatric Comorbidities

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Hepatitis C is one of the most common chronic infectious diseases worldwide, with well-documented extra-hepatic manifestations, such as a broad number of cognitive deficits. These impairments may be explained by psychiatric comorbidities, which have not been investigated properly in the literature. In order to elucidate a specific hepatitis C virus (HCV) induced cognitive impairment not related to mental disorders, neuropsychological performance of patients infected with HCV was compared with that of patients infected with hepatitis B virus cognitive impairment, especially psychiatric comorbidities. A total of 33 patients infected with HCV and 22 patients infected with HBV were included in the study. There were no significant differences between the two groups with regard to age or years of education. The group of patients infected with HCV performed significantly worse on visuo-spatial memory tasks after adjusting for years of education and age. There were no significant differences between patients infected with HCV and patients infected with HBV with regards to other neuropsychological functions. The data indicate that patients infected with HCV patients have poorer visuo-spacial memory performance than patients infected with HBV, suggesting that the cognitive deficit may be specific to HCV infection and not to secondary comorbid psychiatric disorders. ***J. Med. Virol. 81:1184–1188, 2009.*** © 2009 Wiley-Liss, Inc.

**KEY WORDS:** hepatitis C virus; cognitive dysfunction; chronic liver disease; mental disorders; major depression

## INTRODUCTION

Hepatitis C is one of the most common chronic infectious diseases worldwide, with an estimated global prevalence of 2% [Shepard et al., 2005]. Furthermore, hepatitis C virus (HCV) (family Flaviviridae, genus *Hepacivirus*, species *Hepatitis C virus*) infection is an important cause of cirrhosis and liver transplantation. A sharp increase in the number of infected people with complications is expected in the next decade [Armstrong et al., 2000; McHutchison, 2004]. Additionally, HCV infection itself is associated with extrahepatic complications that may have an additional impact on the quality of life of patients with hepatitis C [Quarantini et al., 2008]. One extra-hepatic manifestation, in advanced forms of the disease, is hepatic encephalopathy that can result in a broad number of cognitive deficits [Weissenborn et al., 2001; Pantiga et al., 2003; Mattarozzi et al., 2005]. Recently, many studies have found that patients infected with HCV, even in the absence of clinically significant liver disease, often

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complain of fatigue, depression, forgetfulness, and difficulty concentrating [Forton et al., 2002; Hilsabeck et al., 2002; Weissenborn et al., 2004, 2005; Collie, 2005; McAndrews et al., 2005]. In addition, these patients performed poorly using a larger number of neuropsychological tests than did individuals who were not infected with HCV [Forton et al., 2001; Thein et al., 2007]. However, although most studies have documented cognitive deficits in patients with HCV, different confounders, such as psychiatric comorbidities, might be the primary explanation for these impairments [Perry et al., 2008].

Neurocognitive impairments in major depressive disorder have been reported formeasures of executive functioning [Merriam et al., 1999; Schatzberg et al., 2000], verbal and non-verbal learning [Basso and Bornstein, 1999], sustained vigilance [Dunkin et al., 2000; Sheline, 2000; Landro et al., 2001], visuo-motor attention [Albus et al., 1996; Porter et al., 2003] and visuo-spatial processing [Coello et al., 1990; Bulbena and Berrios, 1993; Henriques and Davidson, 1997; Porter et al., 2003].

The main objective of the present study was to compare the neuropsychological profile of patients infected with HCV with that of patients infected with the hepatitis B virus (HBV) (family Hepadnaviridae, genus *Orthohepadnavirus*, species *Hepatitis B virus*), and thus address the issue of whether cognitive impairment is specific to HCV by excluding potential confounders, especially psychiatric comorbidities.

## METHODS

### Participants

Outpatients infected with HCV or HBV, aged 18–65, were eligible for the study. Exclusion criteria included current treatment with psychotropic medication, mental retardation, dementia, seizure disorder, stroke, neurovascular disease, current axis I psychiatric disorders in accordance with the Diagnostic and Statistical Manual of Mental Disorders-IV [American Psychiatric Association, 2000], history of alcohol or substance abuse or dependence in the last 6 months, treatment with interferon alpha in the last 3 months, uncompensated cirrhosis, cancer or other severe medical conditions.

### Study Design

This cross-sectional study was conducted at the University Hospital of Federal University of Bahia, Brazil. The study was approved by the local Medical Ethics Committee. All subjects provided written informed consent after being given a detailed explanation of the study. Participants were selected after a thorough screening of their medical records to identify inclusion and exclusion criteria. Subsequently, the Mini-International Neuropsychiatric Interview, Brazilian version 5.0.0 [Amorim, 2000], a short, structured diagnostic interview using the Diagnostic and Statistical Manual of Mental Disorders (DSM)—revision IV and the International Classification of Diseases (ICD)—10th edition criteria of psychiatric disorders, was performed to exclude patients with axis I psychiatric conditions. Mini-International Neuropsychiatric Interviews were conducted by trained psychiatrists.

***Neuropsychological tests.*** Neuropsychological tests were administered in a silent room with adequate lighting conditions. Participants remained comfortably seated during tests. The neuropsychological battery was administered in the same predetermined order for all participants. The neuropsychological evaluation included:

*Rey Auditory Verbal Learning Test [Diniz et al., 2000].* This test was used to assess verbal learning and memory. In this test, a list of fifteen words (list A) is slowly read five times. Each of the attempts is followed by a test of spontaneous retrieval. The total sum of attempts, from 01 to 05, is calculated. After the fifth attempt, a list of interference, also comprising 15 nouns, is read to the subject. After the list of interference is read, the examiner asks the individual to recall the words from list A, without reading it again (attempt 06). After a 30-min interval, the examiner asks the individual to remember the words from list A (attempt 07) a second time without reading this list.

Rey Auditory Verbal Learning Test measures the ability to learn and retain a series of words, the extent of the verbal memory, susceptibility to distractions, and recall.

*Trail Making Test—Parts A and B [Reitan, 1992].* This test was designed to measure attention, visual searching, mental processing speed, and the ability to mentally control simultaneous stimulus patterns. The Trail Making Test consists of two parts: *Trail Making Test—A* requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet. Task requirements are similar for *Trail Making Test—B*, which, alternately, includes numbers and letters to be connected. The score on each part represents the amount of time required to complete the task.

*Digit Span.* Forward and Backward [Wechsler, 1997]: This test was used for evaluation of working memory and short-term memory. It involves repeating a series of digits presented orally to the participant at the rate of one digit per second, according to standard procedures. Participants are asked to repeat the digits in both the order that they were presented and in the reverse order.

*Rey–Osterieth Complex Figure [Meyers et al., 1996].* This test assesses perceptual organization, visuo-spatial constructional ability, and visual memory.

Subjects are shown the Rey–Osterieth Complex Figure and asked to copy it as accurately as they can. Next, a filler task is given and then subjects are asked, without knowing ahead of time, to recall as much of the figure as they can. Scores are obtained immediately after the filler task and 30 min after the copying task.

### Statistical Analysis

Data were registered and analyzed using the Statistical Package for Social Sciences (SPSS for Windows, version 10.0). Proportion differences were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared with Student's *t*-test or Mann–Whitney test for non-parametric data.

Neuropsychological performance of patients infected with HCV or HBV was evaluated using analysis of covariance (ANCOVA) with neuropsychological measures as within-subject factors, hepatitis infection agent (HCV vs. HBV) as a between-subject factor, and age and level of education (scored in years) as covariates.

Because of the exploratory nature of the study, corrections were not performed for multiple comparisons. For all statistical analyses, significance was set at $P < 0.05$, two-sided.

## RESULTS

A total of 33 patients infected with HCV and 22 patients infected with HBV = were included in this study. There were no significant differences between groups with regard to gender, age or years of education (Table I).

Patients infected with HCV performed poorly on Rey–Osterieth Complex Figure immediate recall ($P = 0.004$) and showed a tendency to perform poorly on Rey–Osterieth Complex Figure delayed recall in comparison to patients infected with HBV ($P = 0.07$). There were no significant differences between groups with Rey Auditory Verbal Learning total score, Rey Auditory Verbal Learning delayed recall, Digit Span Forward, Digit Span Backward, or Trail Making Test A and B (Table II).

## DISCUSSION

In the present study, a neuropsychological test was administered to patients infected with HCV and HBV in order to measure visuo-spacial memory and executive function. Those patients infected with HBV had better performance on this test than those patients infected with HCV. This difference was statistically significant. Additionally, there were no differences between these two groups when evaluating cognitive domains such as attention, verbal memory, working memory, and learning. In keeping with previously reported findings, the present study found HCV infection to be related to cognitive deficits, independent of liver dysfunction [Forton et al., 2001, 2002; Hilsabeck et al., 2002, 2003; Weissenborn et al., 2004; Fontana et al., 2005; McAndrews et al., 2005]. In previous studies, however, the presence of psychiatric comorbidity may have been a significant confounder. This is relevant because only a small number of studies have found no significant differences between depressed patients and health controls in short-term and working memory [Purcell et al., 1997, 1998] and attention [Albus et al., 1996; Sweeney et al., 2000]. In addition, psychiatric morbidity is known to be higher among patients infected with HCV when compared to the general population [Yovtcheva et al., 2001; el-Serag et al., 2002; Batista-Neves et al., 2008; Saunders, 2008] and the presence of mental disorders at the time of neuropsychological evaluation may be a factor contributing to the poorer cognitive performance found in this population [Weissenborn et al., 2004; Perry et al., 2008].

Other confounders that may explain, at least partially, the cognitive impairment of patients infected with HCV are lifestyle factors, such as substance abuse [Ersche et al., 2005; Rosenbloom et al., 2005]. For those reasons, we excluded all patients with current axis I psychiatric disorders or recent history of substance misuse from our sample and a group of patients infected with HBV was used as comparison subjects in the present study.

HCV has been detected in the human brain tissues [Murray et al., 2008]. However, few information is available about the pathophysiology of cognitive impairment observed in patients infected with HCV with minimal liver disease. Converging evidence has demonstrated that patients infected with HCV have a pattern of neurocognitive deficits suggestive of frontal-subcortical dysfunction [Hilsabeck et al., 2002, 2003; Perry et al., 2008]. Based on magnetic resonance spectroscopy findings, it was hypothesized that these patients may develop an encephalitis, similar to the pattern reported for patients infected with HIV [Forton et al., 2001]. Another possible contributor to cognitive impairment in chronic hepatitis C is the activation of cytokines [Wilson et al., 2002; Lee et al., 2004; Meyers et al., 2005]. It is well established that once an individual

TABLE I. Demographic Characteristics of the Patients by Group

| Characteristic | Hepatitis infection agent | N | Mean | SD | *P*-value[a] |
|---|---|---|---|---|---|
| Gender—male (%) | HBV | 12 (54.5) | | | 0.609 |
| | HCV | 18 (54.5) | | | |
| Age | HBV | 22 | 34.45 | 11.734 | 0.103 |
| | HCV | 33 | 39.39 | 10.183 | |
| Years of education | HBV | 21 | 8.48 | 2.960 | 0.153 |
| | HCV | 33 | 9.70 | 3.046 | |

HBV, hepatitis B virus; HCV, hepatitis C virus; N, number; SD, standard deviation.
[a]Value for comparisons HBV versus HCV.

TABLE II. Performance of HCV-Infected Patients (n = 33) and HBV-Infected Control Patients (n = 22) in Neuropsychological Tests

| | HCV-infected group | | HBV-infected group | | |
|---|---|---|---|---|---|
| Neuropsychological test | Mean | SD | Mean | SD | *P*-value |
| TMT-A | 57.42 | 39.58 | 47.14 | 20.67 | 0.258 |
| TMT-B | 195.90 | 203.13 | 108.67 | 48.83 | 0.422 |
| Digit span | 5.42 | 2.63 | 4.82 | 2.22 | 0.831 |
| ROCF | | | | | |
| Copy | 46.97 | 37.29 | 61.90 | 38.16 | 0.598 |
| Recall—immediately after copy | 19.38 | 22.99 | 37.14 | 29.01 | 0.004* |
| Recall—30 min after copy | 22.50 | 25.14 | 32.37 | 27.81 | 0.07 |
| RAVLT | | | | | |
| Sum of scores from attempts 01 to 05 | 43.61 | 8.67 | 41.41 | 7.50 | 0.20 |
| Attempt 06 | 8.03 | 2.28 | 8.59 | 2.68 | 0.111 |
| Attempt 07 | 22.50 | 25.14 | 32.37 | 27.81 | 0.874 |

SD, standard deviation; HCV, hepatitis C virus; HBV, hepatitis B virus; RAVLT, Rey Auditory-Verbal Learning Test (the total sum of attempts, from 01 to 05); TMT, Trail Making Test; ROCF, Rey–Osterieth Complex Figure.
*$P$-value $<0.05$ HCV compared HBV (analysis of covariance with age and level of education [scored in years] as covariates).

is infected with HCV, cytokines such as interleukin-2, interleukin-4 and interferon-gamma are released [Cacciarelli et al., 1996], and may continue to be released for years. During the time of infection, certain cytokines such as tumor necrosis factor-alpha (TNF-a) may cross the blood-brain barrier and affect brain activity [Farkkila et al., 1984; Shibata and Blatteis, 1991; Pan et al., 1999]. It has been demonstrated that cytokines have neuromodulatory effects on the brain through the stimulation of neuroendocrine pathways [Wilson et al., 2002; Wrona, 2006]. Cytokines may affect brain functioning indirectly through the vagus nerve and binding to the cerebral vascular endothelium and the induction of secondary messengers [Licinio et al., 1998; Kronfol and Remick, 2000].

This study has some limitations: (1) the small sample size selected in a tertiary center; (2) the restrictive exclusion criteria adopted may explain the dysfunction limited to the visuo-spatial domain when compared with other studies, which demonstrated a broader cognitive impairment [Forton et al., 2001, 2002; Hilsabeck et al., 2002, 2003; McHutchison, 2004; Weissenborn et al., 2004; Fontana et al., 2005; McAndrews et al., 2005]; (3) the lack of a control group without any infectious diseases; and (4) the lack of other specific executive function evaluations. However, this investigation may be relevant to differentiate the specific type of cognitive disturbance that impacts the Rey–Osterieth Complex Figure scores. In summary, the current study adds to the evidence that HCV infection contributes to cognitive impairment, even when important confounders are taken into account. Future controlled studies using a larger sample size are warranted to verify the nature and severity of cognitive deficits related to chronic HCV infection.

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