



Full Length Research Paper

Assessment of cognitive functions in patients with chronic liver diseases using neuropsychological test battery

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Abstract

Cognitive dysfunction has been observed in a range of liver diseases including chronic hepatitis C virus. Such dysfunction may range from mild cognitive changes to overt hepatic encephalopathy. The main purpose was to assess the type of neuropsychological deficits observed in patients with HCV. We further address the issue of whether cognitive impairment is HCV specific, by comparing neurocognitive performance in HCV and HBV patients. The current study assessed 50 HCV patients using standardized neuropsychological measures and compared them with 22 HBV infected patients and 20 healthy controls. The Study participants underwent a comprehensive neuropsychological battery to assess functioning in the areas of visuospatial, naming, attention, memory, verbal fluency, orientation abstraction, and also depression, and anxiety questionnaires were completed. Chronic HCV and HBV patients performed significantly worse than healthy controls in MoCA scores especially in attention, naming, memory, fluency, abstraction and orientation (dominant hemisphere functions). They also had more depression and anxiety. Hepatitis C and hepatitis B patients were similarly impaired in cognitive function. HCV patients cognitive capacity (MoCA and MADRS scores) were significantly associated with liver disease severity as indicated by fibrosis stage. We conclude that chronic HCV infection is accompanied by impairment of cognitive functions. This dysfunction does not appear to be HCV specific, as HBV patients were found to be similarly impaired.

Keywords: HCV, HBV, cognitive function, depression, anxiety.

INTRODUCTION

Infection with the hepatitis C virus (HCV) constitutes a major health problem worldwide, since it is associated with significant morbidity (Hilsabeck et al., 2003). It is well established that advanced forms of the disease are accompanied by overt and global cognitive deficits (hepatic encephalopathy) (Mattarozzi et al., 2005). In addition, 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 (Weissenborn et al., 2005).

Among chronic hepatic diseases, hepatitis B virus (HBV) constitutes a nosological entity that resembles hepatitis C as far as pathogenesis and clinical manifestations are concerned. Consequently, the perspective of using hepatitis B patients as a control

group would expand our knowledge regarding hepatitis-related cognitive decline, shedding more light on the possible pathogenetic mechanism (Assimakopoulos et al., 2007).

Neurocognitive impairment in major depressive disorder have been reported for measures of executive functioning (Schatzberg et al., 2000), verbal and non-verbal learning (Basso et al 1999), visuo-motor attention and visuo-spatial process (Porter et al., 2003).

Early identification of the cognitive manifestations of liver disease is important for both patient monitoring and timing of treatment, and it is now recognized that cognitive assessment may provide useful outcome measures in clinical trials (Ferenci et al., 2002).

The main purpose was to assess the type of neuropsychological deficits observed in patients with

HCV. We further address the issue of whether cognitive impairment is HCV specific, by comparing neurocognitive performance in HCV and HBV patients.

PATIENTS AND METHODS

This study was undertaken at the virology and neuropsychiatry clinics of Minia University Hospital, Minia, Egypt from January 2011 to June 2012. A total of 92 eligible patients were approached to participate. Of these 50 with HCV infection, 22 with HBV infection and 20 healthy controls were randomly selected. Hepatitis C diagnosis was based on HCV-RNA detection in patients' sera by reverse transcriptase polymerase chain reaction (RT-PCR; Amplicor HCV, Roche Diagnostics; USA). PCR products were obtained using 25 μ L reactions (16.5 master mix and 8.5 RNA). The amplification conditions were performed as follows: 95 °C for 10 min, followed by 40 cycles for 15 seconds at 95°C, for 60 seconds at 60 °C and for 90 seconds at 72 °C, and ending with a single 10 min extension step at 72°C (Applied Biosystem, U.S.A). For undetectable HCV RNA the value 50 IU/mL Liver biopsy results and the METAVIR score were recorded for every patient. Hepatitis B diagnosis was based on hepatitis B core antibody (anti-HBc Ab) using commercially Diagnostics anti-HBc EIA enzyme-linked immunosorbent assay (DIASORIN, Italy) and on viral load (HBV-DNA) measurement by PCR (Real Time PCR System CA; USA). Extraction of HBV DNA by using the fully automated QIA. Cube instruments & specific tests; Qiagen Column (QIAamp[®] MinElute[™] Virus Spin Protocol) Qiagen Incorporation according to the manufacturer's Protocol. HBV quantitation by (QIAamp[®] MinElute[™] Virus Spin Protocol) on step 1 Real Time PCR instrument.

Participants were selected after thorough screening of their medical records to exclude any potential risk factors for cognitive impairment. We used the following exclusion criteria: illicit drug use or alcohol abuse, current treatment with psychotropic medication, stroke, cancer, cerebrovascular disease, mental retardation, dementia, seizure disorder, other chronic liver disease, cirrhosis Child B/C, and hepatic encephalopathy.

The study protocol was approved by the Institutional Review Board of the Minia University Hospital and all participants gave written informed consent before entering the study.

All patients underwent the following:

- Thorough abdominal and Neurological examination.
 - Routine investigations as Liver function tests and complete blood picture
 - Abdominal ultrasound to exclude hepatic cirrhosis and hepatic focal lesions
 - Electroencephalography (EEG) was done to all patients using 16 channel digital Nihon Kohden machine.
- Participants were subsequently, subjected to the Mini-International Neuropsychiatric Interview. Interviews were conducted by trained psychiatrists. The neuropsychological battery was administered in the same predetermined order for all participants. The neuropsychological evaluation included:

1. Montreal Cognitive Assessment (MoCA):

A cognitive screening tool with proven validity to assist in the detection of mild cognitive impairment (MCI) (Nasreddine et al., 2003). The final version of the MoCA used in this study is a 30-point test, including short-term memory recall, executive function tests, sustained attention task, serial subtraction task, digits forward and backward, language tasks, and orientation to time and place (Nasreddine et al., 2005).

2. Mini Mental State examination (MMS)

MMS is used to assess: Orientation to time and place, Instantaneous recall, Short term memory, Serial subtraction or reverse spelling, Constructional capacities (copying a design) and Use of language (Folstein et al., 1975).

3. Montgomery-Åsberg Depression Rating Scale (MADRS)

MADRS is designed to measure the degree of severity of depressive symptoms. It is a 10-item checklist. Since there is a comparative lack of emphasis on somatic symptoms, the scale is useful for the assessment of depression in people with physical illness. The following mean scores correlates with global severity measures: very severe, 44; severe, 31; moderate, 25; mild, 15; and recovered, 7 (Montgomery et al., 1979).

4. The Hamilton Anxiety Scale (HAS)

It is a 14-item test measuring the severity of anxiety symptoms. For the 14 items, the values on the scale range from zero to four; according to the severity of anxiety. The total anxiety score ranges from 0 to 56. Persons with generalized anxiety disorder and panic disorder tend to have a total anxiety score of above 20 (Hamilton, 1960).

Statistical Analysis

The advanced statistical package for social science [SPSS] for MS windows (version 11.0) was utilized to furnish the statistical analysis for the study. Simple descriptive statistical tests (Mean and Standard deviation) are used to describe the numerical values of the sample. To test the 2-tailed significance of differences in means, Student t-test for independent samples for 2 groups and one-way analysis of variance (ANOVA) test for comparison between more than 2 groups were used and spearman correlation test. A probability of (p) $\leq$ 0.05 is accepted as significant.

RESULTS

Fifty patients who serologically, virologically and biochemically confirmed hepatitis C and 22 patients infected with HBV (anti-HBc positive) in addition to 20 healthy subjects as a control group were enrolled in this study. EEG was normal in 18 patients, and showed

Table 1. Socio-demographic, pathological and laboratory characteristics of studied subjects

	HCV N =50	HBV N =22	Control N=20	P value ^a
Age (mean+-SD)	42.39 ± 9.96	39.3 ± 10.9	40 ±10.1	0.19
Gender				
Male	38 (76%)	18 (81.8)	12 (60%)	0.06
Female	12 (24%)	4 (18.2%)	8 (40%)	
Years of education	8.70 ±3.9	7.38± 2.9	10.4±1.8	0.13
Viral load (copies/ml), median (IQR)	40.659 (12 231-300 609)		22.018 (80001300)	0.01 [*]
* Fibrosis METAVIR score, n (%)				
F1-F2	36 (72%)			
F3 -F4	24 (28%)			
ALT level, median (IQR))	62 (13-95)	44 (12-112)	23 (9-23)	0.03 [*]

HBV:hepatitis B virus; HCV: hepatitis C virus; IQR: interquartile range.

* Liver biopsy done for HCV patients only.

^a Value for comparisons HBV and HCV versus control only regarding age, sex , serum ALT levels and years of education

epileptic form changes in 8 patients; one of them had right focal changes, five showed left focal changes and two with generalized epileptic form changes. None of our patients had triphasic waves. And no significant difference in cognitive functions between patients with normal or epileptic form EEG changes (data not shown)

Socio-demographic data of the patients and controls were shown in Table 1. There were no significant differences between groups with regard to age, gender or years of education. In addition, HCV and HBV patients differ significantly in viral load indicated by PCR and the serum ALT levels were significantly high in HCV and HBV patients versus the controls.

Regarding neuropsychological tests the HCV and HBV patients performed significantly worse than controls in total MoCA score (0.001; 0.005, respectively) indicating mild cognitive impairment (MCI). Naming, memory, attention, Language, fluency, abstraction and orientation (dominant hemisphere functions) were the most affected domains. Visuospatial function and concentration were lower among all patients versus the control but this difference was statistically insignificant. In addition, HCV and HBV patients differed significantly in MMS versus the controls (P=0.003; P=0.011, respectively).

The mean score of MADRS and HAS were significantly higher in HCV and HBV groups than controls (P=0.003; P=0.001 and P= 0.12; P= 0.022, respectively). MADRS scores ranged between zero and 32 (mean=20.42 ±13.62) MADRS was normal in 32 patients, another 5 had recovered depression, 15 mild, 10 moderate and 10 had severe depression, while none of our patients had very severe depression Table 2.

With HAS scores there is significant statistical difference between all groups. HAS scores ranged between zero and 29 (mean=11.46±9.11), only 6 patients had scores above 20 which signify anxiety. While 24 were completely normal and the rest of patients had insufficient scores to diagnose anxiety.

HCV infected patients performed poorly all psychometric tests in comparison to HBV patients but the significant differences recorded in MADRS and HAS scores (P=0.001; P=0.051) but not with MoCA or MMS scores.

Correlations between clinical parameters and neuropsychological performance in HCV patients were tested. We found significant correlations of liver fibrosis stage with MoCA and MADRS scores (r= 0.40, P=0.01 and r=0.60, P=0.03, respectively). In contrast, level of

Table 2. Comparison between patients with HCV, HBV and Control as regards neuropsychological tests.

Neuropsychological test	HCV	HBV	Control	P value for Comparisons		
				HCV vs HBV	HCV vs control	HBV vs control
MoCA	22.5±4.2	25.2±2.40	38.2± 1.42	0.409	0.005*	0.001**
Visuospatial	2.46±1.65	3.52±1.5	4.77±1.9	0.794	0.450	0.131
Naming	2.50±0.76	2.77±0.43	4.87±0.02	0.531	0.034*	0.011*
Memory	3.53±0.90	4.39±0.7	6.33±0.73	0.093	0.025*	0.002*
Concentration	0.88±0.32	1.23±0.1	1.40± 0.05	0.160	0.372	0.951
Attention	2.30±1.04	2.80±0.4	5.87±0.41	0.437	0.059*	0.012 *
Language	1.50±0.64	1.97±0.3	3.85±0.3	0.295	0.026*	0.007*
Fluency	0.50±0.45	0.79±0.4	1.87±0.44 *	0.108	0.026*	0.003 *
Abstraction	0.84±0.67	1.60±0.5	2.91± 0.58	0.064	0.041*	0.002*
Orientation	2.30±0.88	2.94±0.3	5.85±0.35	0.133	0.011*	0.001*
MMS	22.1±4.7	27.4±1.6	47.2±2.6	0.115	0.011*	0.003*
MADRS	13.4±11.6	8.4±3.2*	2.90±.02	0.011*	0.001*	0.003*
HAS	5.4±7.9	4.8±3.1	1.2±0.8	0.051 *	0.022*	0.012 *

HAS Hamilton anxiety scale, **MADRS**:Montgomery-Åsberg Depression Rating Scale, **MMS**: minimal state,

MoCA: Montreal cognitive assessment,

SD: standard deviation, HCV: hepatitis C virus, HBV: hepatitis B virus.

*P-value <0.05

Table 3. Correlations between neuropsychological tests and laboratory variables in HCV patients.

neuropsychological tests	A L T		Viraemia		Fibrosis	
	r	P	r	p	r	P
MOCA	0.55	0.45	0.30	0.80	0.40	0.01*
MMS	0.66	0.11	0.15	0.14	0.22	0.61
MADRS	0.46	0.15	0.11	0.6	0.60	0.03*
HAS	0.98	0.11 *	0.16	0.4	0.55	0.33

ALT: alanine aminotransferase, **HAS** :Hamilton anxiety scale, **MADRS**: Montgomery-Åsberg Depression Rating Scale, **MMS**: minimal state, **MoCA**: Montreal cognitive assessment, HCV: hepatitis C virus.

* Statistically significant at p <0.05

viraemia and ALT level didn't correlate with any measure of cognitive performance (Table 3). Also this study reported that there was no correlation between depression, anxiety severity, level of education and neuropsychological test scores in HCV patients (Table 4).

DISCUSSION

In the present study, a neuropsychological test was administered to patients infected with HCV and HBV in

order to measure the type and degree of cognitive dysfunction. Chronic HCV patients performed significantly worse than healthy controls in all neuropsychometric tests. Also those patients infected with HBV had better performance than those patients infected with HCV but the difference not statistically significant in MoCA only. There were no differences between these two groups when evaluating cognitive domains such affection was

Table 4: Correlation coefficients of depression, anxiety severity, level of education and neuropsychological test scores in HCV patients

	MOCA		MMS	
	r	P	r	P
HAS	-0.21	0.255	-0.69	0.029
MADRES	-0.07	0.709	-0.30	0.100
Level of education	0.14	0.460	0.07	0.689

HAS: Hamilton anxiety scale, **MADRS:** Montgomery-Åsberg depression Rating Scale, **MMS:** minimal mental state, **MoCA:** Montreal cognitive assessment, HCV: hepatitis C virus.

*P-value <0.05 is significant, all comparisons were not significantly different

higher in dominant hemisphere functions; Visuospatial; attention, naming, memory, Concentration, Language; fluency, abstraction, orientation. This is in agreement with Forton (Forton et al., 2002), who confirmed the presence of cognitive impairment in patients with histologically mild HCV infection. The HCV-infected group scored significantly worse on the power of concentration and on the speed of memory processes than the healthy controls. Other studies have suggested that neurocognitive abnormalities may be seen in this population, with particular deficits in attention, concentration, and information processing (Hilsabeck et al., 2002).

Former studies have compared HCV with HBV patients in terms of quality of life (QOL) and magnetic resonance images and have revealed significant differences (Hilsabeck et al. 2003). However, these parameters have not been clearly associated with hepatitis patient's cognitive function (Weissenborn et al., 2004).

There is substantial evidence that HBV is associated with changes in quality of life and psychological variables as depression and anxiety suggesting that there may well be a cognitive impairment in these patients. However, to the author's knowledge, no published studies have directly addressed the issue of cognition in HBV (Younossi et al., 2001).

Depressive and anxiety symptoms have been reported to be common in patients with untreated hepatitis C infection. The results of this study reveal that both HCV and HBV patients had high frequency of some degree of depression and Hepatitis C patients had more depressive features than hepatitis B patients. These results are in accordance with a previous study that demonstrated Hepatitis C patients had more depressive features than HBV one (Qureshi et al., 2012).

Also several studies showing that HCV infection is associated with increased depression, fatigue, and impaired quality of life. Others found mood disorders in 38% of HCV patients and anxiety disorders in 9% (Yovtcheva et al., 2001). In another study, hepatitis C

patients exhibited more anxiety, depression and mood disorders in comparison with other liver diseases (Wessley et al. 2002). It has also been demonstrated that the quality of life is lower in CHC patients as compared to HBV patients (Foster et al., 1998).

We further examined the associations between HCV disease severity indices and neuropsychological performance. HCV patients' neuropsychological impairment did not correlate with level of viraemia and serum ALT levels which is in line with previous research (McAndrews et al., 2005). In contrast, we found significant associations between liver fibrosis stages and MoCA, replicating the findings of an earlier study (Hilsabeck et al., 2002) in which cognitive performance was associated with fibrosis, suggesting that attention memory, and concentration may be affected early in the course of liver disease liver fibrosis is known to affect liver function and portal pressure, which might, in consequence, exert subtle metabolic effects on the brain (Fowell et al., 2006).

The pathogenesis of HCV-related cognitive decline remains to be defined. Recent studies have shown significant alterations in the brain metabolism of hepatitis C patients that are characteristic of CNS inflammation and indicate a biological influence of HCV on brain tissue (Kramer et al., 2002). Several mechanisms have been proposed implicating a direct action of the HCV on cerebral tissue (Laskus et al., 2005) or an indirect influence via activation of intracerebral immune response or circulating cytokines (Forton et al., 2003). Psychological distress and fatigue might also influence cognitive performance, given their high prevalence in people infected with HCV (Kramer et al., 2002).

Converging evidence has demonstrated that patients infected with HCV have a pattern of neurocognitive deficits suggestive of frontal-subcortical dysfunction (Perry et al., 2008). Based on magnetic resonance spectroscopy findings, it was hypothesized that these patients may develop 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 (Meyers et al., 1996). During the time of infection, certain cytokines such as tumor necrosis factor- α (TNF- α) may cross the blood-brain barrier and affect brain activity. It has been demonstrated that cytokines have neuromodulatory effects on the brain through the stimulation of neuro-endocrine pathways (Wrona, 2006). Cytokines may affect brain functioning indirectly through the vagus nerve and binding to the cerebral vascular endothelium (Kronfol et al., 2000).

In conclusion, these findings suggest that chronic HCV infection is accompanied by impairment of cognitive functions in the absence of hepatic encephalopathy. This dysfunction does not appear to be HCV specific, as HBV patients were found to be similarly impaired. HCV-related cognitive deficits were associated with liver fibrosis but did not relate to liver enzymes or viraemia. Moreover, it would be interesting to further investigate the degree and the type of cognitive impairment observed in hepatitis C as well as in hepatitis B and other chronic liver disease patients, using advanced neuro-imaging and neurophysiology techniques, in order to elucidate possible pathogenic mechanisms.

CONCLUSION

We conclude that chronic HCV infection is accompanied by impairment of cognitive functions. This dysfunction does not appear to be HCV specific, as HBV patients were found to be similarly impaired.

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