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¹Hepatitis C virus antibody titers associated with cognitive dysfunction in an asymptomatic community based sample

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Abstract

Background—Hepatitis C virus (HCV) infection is associated with cognitive dysfunction in clinic-based studies. The risk could be attributed to factors such as antiviral medications, substance abuse or coincidental infection.

Aim—To evaluate cognitive function in relation to HCV antibody titers in a community-based sample of asymptomatic individuals at low risk for substance abuse.

Methods—Adults were ascertained from a community in Mansoura, Egypt, where HCV is endemic (n=258). Cognitive performance was evaluated using the Arabic version of the Penn computerized neurocognitive battery. Substance abuse and psychopathology were also assessed. Antibodies to HCV and Toxoplasma Gondii (TOX), a common protozoan that can affect cognition were estimated using serological IgG assays.

Results—The prevalence of HCV and TOX infection was 17.6% and 52.9%, respectively. HCV antibody titers were significantly associated with worse function in four cognitive tests for accuracy and three tests for speed, after adjusting for covariates ($p < 0.05$, beta coefficients, 2.1-3.2). TOX antibody titers were associated with impaired accuracy in one test.

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Conclusions—The association between HCV antibody titers and cognitive impairment is not mediated by antiviral treatment or substance abuse in this sample. Whether HCV has a causal role in the cognitive dysfunction should be investigated.

Keywords

HCV; Cognition; toxoplasma; CNB

Introduction

HCV is the second most common blood-borne disease in the world, affecting up to 2% of the world's population. It is also a leading cause of cirrhosis and liver cancer (Alter et al., 1999; Shepard, Finelli, & Alter, 2005) (Armstrong, Alter, McQuillan, & Margolis, 2000). HCV infection can be associated with cognitive dysfunction, but the association itself and the basis for the association are controversial (Abrantes, Torres, & Mello, 2013; Gaeta, Di Paolo, Fasanaro, & Loguercio, 2013; Perry, Hilsabeck, & Hassanein, 2008; Senzolo et al., 2011). Though initially attributed to hepatic encephalopathy, cognitive dysfunction has also been noted prior to onset of liver dysfunction (Forton et al., 2002). The HCV-associated cognitive dysfunction has been attributed to psychiatric morbidity or intravenous substance abuse that are more prevalent among patients infected with HCV compared with population rates (Batista-Neves et al., 2009; El-Serag, Kunik M, Richardson P, & Rabeneck, 2002; Perry et al., 2008; Saunders, 2008). Others have pointed to antiviral drugs used to treat HCV infections as those drugs can increase rates of depression and associated cognitive dysfunction (Reichenberg, Gorman, & Dieterich, 2005). The relatively high co-morbidity between HCV infection and psychopathology, particularly with intravenous substance abuse in economically advanced countries makes it difficult to conclude whether HCV infection *per se*, or other infection-related confounding variables mediate the putative cognitive dysfunction.

It would be informative to investigate HCV-related cognitive dysfunction in Egypt, where the prevalence of HCV is relatively high (~15%), partly due to inadequately sterilized needles that were used to administer parenteral medications during past public health campaigns against schistosomiasis (El-Zanaty & Way, 2009; Nafeh et al., 2000; Rao et al., 2002; Zakaria et al., 2007). In addition, intravenous drug abuse is uncommon in Egypt and does not represent a major risk of HCV transmission (Zakaria et al., 2007), though needle stick injuries among health care workers and minor medical procedures performed by inadequately trained rural health care providers are minor risk factors (El Katsha S, Labeeb S, Watts S, & A., 2006; Talaat et al., 2003; Zakaria et al., 2007). We therefore evaluated the association between HCV exposure and cognitive function, in conjunction with psychiatric evaluations in the Nile delta region of Egypt. We reasoned that the estimates from a community-based sample would be more generalizable than a clinic based sample. We also estimated exposure to Toxoplasma Gondii (TOX), a protozoan parasite that infects over 50% of adults in Egyptian, as TOX too has been associated with cognitive dysfunction and some psychiatric disorders (El Deeb, Salah-Eldin, Khodeer, & Allah, 2012; Elsheikha et al., 2009; Hussein, Ali, Saleh, Nagaty, & Rezk, 2001) (Fabiani, Pinto, & Bruschi, 2013). We report that HCV is associated with dysfunction in several cognitive variables, in contrast to TOX.

METHOD

Design

We conducted a cross-sectional study in a community-based sample. As increasing age is associated with cognitive impairment as well as higher levels of antibodies to infectious agents (Mattson, 2004), we over-sampled adults in three age bands to ensure an adequate distribution of participants across the adult lifespan. The study was approved by the Ethics community of Mansoura University and the University of Pittsburgh IRB. All participants provided written informed consent.

Site—The study was conducted at an electricity generating company in Mansoura Egypt. To sample older persons who had retired, we also recruited older participants from a café club. Recruitment started August 2012 and ended in February 2014.

Methods

Participants—We included Egyptians of both genders whose age ranged from 21-62 years old, in three age bands: 21-32, 38-42, and 55-62 years of age. We excluded those with psychiatric disorders, current alcohol / illicit substance abuse or substance abuse in the past 6 months (DSM IV criteria), inability to read and write, a history of learning disability and participants with severe medical conditions that would affect cognitive performance; e.g., liver cell failure, epilepsy, history of encephalitis or severe head trauma, or any other reported disorder of the central nervous system.

Clinical assessment—The Arabic version of the Standard for Clinicians' Interview in Psychiatry (SCIP) (Aboraya et al., 2014), a semi-structured diagnostic interview schedule was completed by all participants. Information gathered with the SCIP was used to assess psychiatric diagnostic exclusion criteria. Sociodemographic data including age, sex, residence, occupation, handedness, level of education and marital status were also obtained. A medical history was obtained using a customized questionnaire.

Cognitive assessment—Cognitive functions were assessed with the Arabic version of PENN computerized neurocognitive battery (Penn CNB) (Ibrahim et al., 2015). Unlike pencil and paper assessments, the Penn CNB directly records accuracy and speed of response onto computerized databases, so it is unlikely to be influenced by rater bias (Gur, 2001b). The Arabic Penn CNB consists of 14 tests: Motor Praxis Test (MPRAXIS) for assessment of Sensorimotor integration speed; the Penn Continuous Performance Test – Number (PCPT-n) for assessment of attention; Face memory (immediate and delayed) with the Penn Face Memory Test (CPF) and Penn Face Memory Test Delayed Memory (CPFd); the Penn Conditional Exclusion Task (PCET) for assessment of abstraction and mental flexibility; Short Computerized Finger-Tapping Task (sCTAP) for assessment of spatial memory; Short Visual Object Learning Test (sVOLT) and Short Visual Object Learning Test Delayed Memory (sVOLTd); the Penn Matrix Reasoning Test (PMAT) for assessment of Nonverbal Reasoning; the Short Penn Line Orientation Test (sPLOT) for Spatial orientation; the Age Differentiation Test (ADT) for social cognition; Penn Emotion Recognition Task

(ER40); the Measured Emotion Differentiation Test (MEDF) and finally, the Short Fractal N-Back (SFNB2) for assessment of working memory.

Laboratory assays—Venous blood samples were obtained from all participants and stored at -80°C . IgG antibodies to HCV were assayed in the serum or plasma using a commercial Enzyme Linked Fluorescent Assay at the certified Pathology laboratories of the Mansoura School of Medicine (“<http://www.biomerieux-diagnostics.com/vidas-hepatitis-panel>,”). Seropositivity was defined as HCV antibodies titer >1 as specified by the manufacturer. IgG antibodies to TOX were assayed together using solid-enzyme IgG immunoassays to estimate at the Stanley Laboratory of Developmental Neurovirology, Baltimore, Maryland (Dickerson et al., 2014). Based on the distribution of TOX antibody levels, seropositivity was defined as IgG titer >2 units.

Statistical analysis—Parametric or non-parametric tests were used to compare seropositive and seronegative individuals. Multiple logistic regressions were conducted using the standardized score for each cognitive test as the dependent variable, with HCV antibody titers, TOX antibody titers, age, gender and years of education as independent variables. The SPSS 22 software package was used to analyze all data. Estimates of accuracy and for speed of completion were analyzed separately for each cognitive function. Corrections for multiple comparisons were not employed, as we tested prior reported associations.

Results

Demographic characteristics

The sample included 258 persons (Table 1). Their mean age was 40.61 years (standard deviation, SD 11.24). The level of education ranged from 4 years to 20 years of school/college, mean of 12.76 years (SD 2.85). The prevalence of HCV seropositive and TOX seropositive individuals was 17.6% and 52.9%, respectively. In comparison with the HCV seronegative individuals, the HCV seropositive individuals were older and were more likely to have retired. The TOX seropositive participants were more likely to be married, but there were no significant differences with regard to the other demographic variables that were analyzed. The data from ten participants were not included for further analyses. They included three participants for whom complete clinical data were unavailable and seven other participants who reported prior interferon treatment for HCV infection.

Correlations between HCV antibody titers, toxoplasma antibody titers and cognitive functions

The correlations between the cognitive measures, antibody titers and demographic variables are presented in Supplementary Table 1. There were significant positive correlations between HCV antibody titers and age ($P = 0.0001$), employment ($p < .0001$), and reaction time for four of the cognitive measures. There were significant negative correlations between HCV antibody titers and years of education ($p = 0.003$), and accuracy of five of the cognitive measures. There was significant positive correlation between TOX antibody titers and the reaction time for Penn conditional exclusion test (speed) only ($p = .036$). There was a

significant negative correlation between TOX antibody titers and the following cognitive variables: Line orientation test (accuracy) ($p = .029$), Measured emotion differentiation (accuracy) ($p = .002$), Emotion recognition (accuracy) ($p = .024$) (see supplemental tables).

Associations between antibody levels and cognitive variables

HCV

Following corrections for age, gender and years of education, HCV antibody titers were negatively associated with speed for the Penn Face Memory Test and Age Differentiation tests. HCV antibody titer was also negatively associated with accuracy for the Penn Continuous Performance Test – Number, Short Penn Line Orientation Test, Penn Matrix Reasoning Test and Age Differentiation test. All the significant associations are listed in Table 2, and the complete models are presented in Supplementary Tables 2 and 3).

TOX

There was a significant negative association between TOX antibody titers and accuracy for the Measured Emotion Differentiation Test.

The HCV positive and negative groups differed in size and mean age. As the regression analyses involving the entire sample might not correct adequately for these differences, we generated two subgroups. First, we listed all the individuals with elevated HCV titers. A second group matched by age and gender to the first group was next generated. When regression analysis were repeated, HCV titer remained a significant negative predictor for the reaction time of the Penn face memory test and the accuracy of the Penn line orientation test (Supplementary Table 5; these associations were also present in the larger sample). Age continued to be a significant positive predictor for the reaction time for six cognitive domains and a significant negative predictor for the reaction time of the Penn Emotion Recognition. Education also remained a significant positive predictor for the accuracy of seven tests.

Discussion

HCV infection, indexed by elevated IgG antibody titers was significantly associated with worse performance in the cognitive domains of nonverbal reasoning, attention, spatial orientation, age identification and working memory. The effects sizes were modest, but the associations are credible because we excluded potential confounding factors in prior reports, such as depression, substance abuse and co-morbid medical disorders. The associations were detected after controlling for TOX infection, which is endemic in Egypt and has been reported to cause cognitive dysfunction, particularly in rodents (**Kannan & Pletnikov, 2012**). Moreover, our sample was composed of relatively healthy individuals recruited from the community. Consistent with our results, a review by Gaeta et al (2013) concluded that HCV patients have significant impairment in accuracy tests of executive functions, memory, recognition and attention (**Gaeta et al., 2013**). Impairment of verbal learning/memory and reasoning/mental flexibility were the most frequently reported impairments (Huckans 2009). Others have also reported dysfunction in immediate and sustained attention, higher executive function, verbal learning ability, verbal recall and working memory (**Perry et al., 2008**;

Senzolo et al., 2011). On the other hand, there are discrepancies in associations with visuospatial memory, auditory attention, speed of visual information processing, and motor functions (Huckans et al., 2009) Hilsabeck et al., 2002) (Forton et al., 2002) Weissenborn et al., 2004).

Psychomotor speed refers to the amount of time it takes a person to process a signal, prepare a response, and execute that response (**Lezak, 2004**). It is a broad, often amorphous, construct that is closely related to attention, because slowed processing speed sometimes underlies attentional deficits (**Lezak, 2004**). Associations between HCV infection and measures of psychomotor speed are variable. Some groups did not detect significant associations (Córdoba et al., 2003; Fontana et al., 2005; McAndrews et al., 2005; Weissenborn et al., 2004), whereas others have suggested that psychomotor speed is one of the most impaired neurocognitive domains among individuals with HCV infections (Forton et al., 2002; Hilsabeck, Hassanein, Carlson, Ziegler, & Perry, 2003). We found that HCV antibody titers is a significant negative predictor for the reaction time in several tests, including the Penn Face memory, Penn face memory delayed and Age differentiation tests that index episodic memory (face memory) and social cognition respectively. The associations may indicate impulsivity (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). A previous study found increased delay discounting and executive dysfunction (conditions commonly associated to impulsiveness) in chronic Hepatitis C (CHC) patients when compared with controls without CHC (**Huckans et al., 2011**). The different patterns of HCV associations could be attributed to variations in patient characteristics (e.g., inconsistent exclusion of other medical and psychiatric comorbidities), the use of different kinds of control groups, relatively small samples, and variable definitions of cognitive impairment definition. Another important difference is that most participants in the published studies were recruited from tertiary care facilities, in contrast to our community sample.

The mechanisms for the HCV related cognitive dysfunctions are uncertain. The association may not reflect liver pathology, as cognitive impairment is not associated with Hepatitis B infection (**Quarantini et al., 2009**). HCV particles have been detected in the brain (Forton, Taylor-Robinson, & Thomas, 2006; Forton, Thomas, & Taylor-Robinson, 2004) and HCV patients have abnormalities in cerebral metabolites and P300 evoked potentials, suggesting direct viral effects on the brain (**Forton et al., 2005; Kramer et al., 2002**). In addition, several studies have reported down regulated mitochondrial oxidative phosphorylation genes and reduced expression of specific ribosomal protein genes in post-mortem brain tissue from HCV+ patients (**Adair et al., 2005**). HCV-associated cognitive dysfunction is not significantly correlated with impaired liver function tests and the impact of antiviral medications for HCV infection is uncertain (Abrantes et al., 2013; Fontana et al., 2005; McAndrews et al., 2005; Weissenborn et al., 2004).

We found that TOX infection was associated with one cognitive variable. Previous studies reports have been contradictory results, with some investigators reporting impaired function (**Gajewski, Falkenstein, Hengstler, & Golka, 2014**), while others did not detect statistically significant effects (**Guenter et al., 2012**) & **Kruszonet al 2014**), (J. Flegr et al., 2012) (Pearce, Kruszon-Moran, & Jones, 2014). One reason for the variability may be the

relatively low prevalence of TOX infection in many economically advanced nations, so relatively large studies of older individuals are required to enable sufficient statistical power (Gajewski et al., 2014). Others have suggested that the associations are stronger in men, possibly due to hormonal effects (J. Flegr et al., 2012) (J. Flegr et al., 2012; J. Flegr, Novotna, Lindova, & Havlicek, 2008).

Some shortcomings of our study should be noted. We did not estimate hepatic functions among the participants, though we excluded individuals who reported current or prior treatment for hepatitis. We did not conduct urine analysis for illicit drugs, though intravenous drug abuse is uncommon in Egypt (Wasley & Alter, 2000). Whether the HCV associated cognitive dysfunction also impairs occupational function is not known. Though infection with HCV is frequently comorbid with HIV infection in many parts of the world, we did not screen for HIV infection because the prevalence of HIV/AIDS is relatively low in Egypt. Results from the Egyptian National AIDS Control Programme Surveillance indicate that the prevalence is approximately 0.03% in the general population and among people with high-risk behaviors, the prevalence ranges from 0.05% to 0.56%. ("Annual AIDS hotline report. Cairo ministry of health and population (Egypt) and national AIDS control programme," 2000).

In conclusion, HCV infection was associated with cognitive dysfunction in several cognitive domains in a community-based sample of adults from Egypt screened for absence of mood disorders or substance abuse. Replicative studies and further investigations of the mechanisms of the associations are needed. It would also be important to know if the cognitive dysfunction is linked to impairment in occupational function or living skills.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic features of participants with and without raised antibody levels.

		Hepatitis C Virus			Toxoplasma Gondii	
		Seropositive (N=38)	Seronegative (N=210)	P	Seropositive (N=134)	Seronegative (N=114)
Age	Mean/ SD	53.18/8.944	38.09/9.996	<0.0001	41.19/11.097	39.48/11.373
Gender	Male/female	36 /2	180 /30	.19	115/19	101/13
Marital_status	Ever Married	37	198	.69	131	104
	Never married	1	12		3	10
Employment_status	Full time paid	30	200	<.0001	121	109
	Part time paid	0	4		3	1
	Household duties	1	3		4	0
	Unemployed	1	1		0	2
	Retired	6	2		6	2
Occupation	Unskilled and semiskilled	21	106	.50	73	54
	Skilled, clerical, semiprofessional	11	80		48	43
	Executives	6	24		13	17

Table 2

Cognitive variables significantly associated with Hepatitis C virus or Toxoplasma Gondii antibody titers.

	Accuracy				Reaction Time			
	HCV antibody titers		TOX antibody titers		HCV antibody titers		TOX antibody titers	
	Beta coefficient	p	Beta coefficient	p	Beta coefficient	p	Beta coefficient	p
Motor Praxis Test					-.091	.096	.038	.442
Penn Face Memory Test	-.039	.574	.024	.695	-.187	.002	.022	.671
Penn Continuous Performance Test–Number	-.158	.015*	-.053	.365	.060	.360	.043	.462
Penn Matrix Reasoning Test	-.180	.006**	-.018	.755	-.136	.051	.056	.368
Short Penn Line Orientation Test	-.153	.016*	-.081	.151	-.073	.241	-.028	.616
Penn Face Memory Test Delayed Memory	.026	.697	-.014	.824	-.137	.033	-.055	.340
Measured Emotion Differentiation Test	-.060	.367	-.149	.013	-.078	.220	.016	.774
Penn Conditional Exclusion Task	.007	.916	-.013	.839	-.074	.231	.068	.223
Short Computerized Finger-Tapping Task	.045	.519	-.080	.199				
Short Visual Object Learning Test	.103	.134	-.049	.425	-.052	.452	-.031	.625
Penn Emotion Recognition Task	.078	.243	-.103	.086	-.080	.194	.042	.454
Short Fractal N-Back	-.137	.052	.003	.959	.012	.864	.003	.959
Age Differentiation Test	-.149	.029*	-.017	.788	-.149	.025*	.019	.756
Short Visual Object Learning Test Delayed Memory	.082	.234	-.080	.202	-.037	.593	-.063	.310

All p values uncorrected for multiple comparisons.