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Effects of hepatitis C and HIV on cognition in women: Data from the Women's Interagency HIV Study

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Abstract

Objective—To compare neuropsychological scores in women infected with HIV, women infected with both HIV and hepatitis C, and uninfected subjects.

Background—Some, but not all, studies have demonstrated that dual infection with HCV and HIV has worse effects on cognition than infection with HIV alone.

Design/Methods—The Women's Interagency HIV Study (WIHS) is an ongoing prospective study of the natural history of HIV in women where participants are reevaluated every 6 months.

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In a cross-sectional analysis, we evaluated the effects of active HIV and HCV-infections on scores on symbol-digit test (SDMT), the Stroop interference test, and trails A and B after controlling for age, ethnicity, education, depression, liver disease, and current or past substance abuse.

Results—Data were available for 1338 women – 17.8 % had detectable hepatitis C virus and 67% were HIV-seropositive. In fully adjusted general linear models, HCV viremia was not associated with scores on any of the cognitive tests.

Conclusion—In this large sample of women, active HCV infection was not associated with scores on a small battery of neuropsychological tests.

Keywords

Hepatitis C; HIV; neurocognition; women

Hepatitis C (HCV) is the most common cause of chronic liver damage in the United States [1]. Many patients are infected with both HCV and HIV; rates of co-infection range from 16–40% with higher rates in intravenous drug abusers [2–3]. In the last decade, several studies have suggested that patients with HCV have a high prevalence of cognitive impairments, and that the effects on cognition are unrelated to hepatic encephalopathy [see reviews within 3,4]. Autopsy studies have shown replicative forms of HCV virus in the brain of some HCV patients [5–7], and brain magnetic resonance spectroscopy studies demonstrated patterns consistent with inflammation in the basal ganglia and white matter [8–9]. Moreover, several studies have suggested that co-infection with HCV and HIV may have worse effects on cognition than monoinfection [10,11].

Nonetheless, most previous series of the effects of HCV and HIV on cognition have been small; often too small to control for the numerous confounding factors that influence cognition. At least 2 larger studies that attempted to control for these confounding factors, did not find a significant effect for HCV infection [2,12]. Women were underrepresented in most previous studies of the effects of HCV and HIV on cognition, and some have suggested that HIV-related cognitive impairment is worse in women [13]. Because HCV is prevalent in the large women's interagency HIV study (WIHS), we assessed the effects of HCV and HIV on cognition in analyses.

METHODS

Cohort

The Women's Interagency HIV Study [14,15] is an ongoing prospective study of HIV in women. The WIHS began in 1994 and has enrolled 3766 women across six sites in San Francisco, Los Angeles, Chicago, Washington, DC, Brooklyn and the Bronx (New York). WIHS initially recruited 2054 HIV-infected and 569 HIV-uninfected women in 1994–95, and an additional 737 HIV-infected and 406-HIV uninfected women in 2001–2002. Participants are evaluated every six months with an extensive interview that includes history of interval illnesses and interval substance abuse, current medications and medication adherence, physical exam, and blood and gynecological specimen collection. Details of standardized data collection protocols and training of interviewers have been previously described [14, 15]. Toxicological testing for illicit substances was not performed. CSF collection has not been a part of WIHS protocols. Data regarding significant past head trauma were not available.

Outcomes

Outcomes/neuropsychological tests—The symbol-digit modalities test (SDMT)[16–17] was administered to all English speaking WIHS participants during visits 21 to 24 (October 2004 to September 2006) as part of the core assessment. The SDMT is a measure of speed of information processing and perceptual motor ability. This substitution test requires participants to use a code table at the top of the page to quickly write the correct digit in an empty box below a symbol with a time limit of 90 seconds. Score was the total number of boxes that were correctly filled within the time limit. Some participants completed the testing on all 4 visits. Only the 1st score is used for each subject. Trails A and B tests [18–19] were also administered to English speaking participants during visits 21 to 24 and again we used results from the first time tested. The Trailmaking Test (Parts A and B) measures processing speed and cognitive flexibility. Part A is a page with 25 numbered circles randomly arranged. Part B is a page with circles containing the letters A through L and 13 numbered circles intermixed and randomly arranged. Participants instructed to draw lines connecting the circles while alternating between numbers and letters in sequential order. Time to completion were the measures used in this report.

We administered the Comalli-Kaplan Stroop [20–21] during visits 25–28, October 2006 to September 2008. Women who spoke Spanish, but not English, did not take the Stroop test. We report condition 3, the interference task. In this test, the words “red”, “blue”, and “green” are printed in red, green, and blue ink, but the meaning of the word and the color of the ink are not always congruent. Subjects have to report the color of the ink. One hundred such words are arranged in rows. Errors were recorded, but we only include time to completion in these analyses. Times greater than 240 seconds were not censored (9 out of 1426 participants had scores greater than 240 seconds).

Cofactors and covariates—Ethnicity was self-reported as described previously [15]. 96.1% of participants described themselves as white, Hispanic, or African-American. We combined the remaining 5 groups into one “other” group (N = 50). Symptoms of depression were recorded with the Center for Epidemiological Studies – Depression scale (CES-D) at every visit [22]. Based on previous work, women were divided into those with scores of ≤ 22 (not depressed or less depressed), and those with scores 23 and higher (more depressed) [23]. As the dates of cognitive testing varied, for multivariate analyses we used the CES-D score closest to the time of neuropsychological testing. We used a history of previous psychiatric hospitalizations as a surrogate for history of serious psychiatric illnesses that could influence cognitive scores.

The HCV group was defined as HCV antibody positive and HCV RNA positive. The HCV negative group was defined as HCV antibody negative.

Education was self-reported on an 8 point scale ranging from 1 – no education to 8 – completed doctoral degree. In this study, the 8 education groups were collapsed into 4 levels: 1) less than completing high school (N = 434), 2) completed high school with no further formal education (N = 349), 3) did not complete undergraduate degree (N = 349), and 4) completed undergraduate degree or higher (N = 100). We assessed reading ability with the Wide-Range Achievement Test (WRAT-3) (24). Our previous work had demonstrated that WRAT-3 usually accounted for more variance in cognitive score than educational level (25).

FIB-4 was calculated by the following formula: age (years) × AST[U/L]/platelets[10⁹/L] × (ALT[U/L])^{1/2} following published methods [26]. AST-to-platelet ratio (APRI) was computed with the following formula: AST level (/Upper Limit of Normal) × (Platelet

Count $(10^9/L))^{-1} \times 100$ following published methods [27]. The APRI and FIB-4 are simple non-invasive measures of liver fibrosis that are consistent with liver biopsy results.

Inclusion criteria—Data presented in this report include all data collected by wave 28, concluding in September 2008 on participants enrolled in the Genetic Predictors of Substance Abuse in HIV substudy. A total of 1426 participants (472 uninfected and 954 HIV-infected) completed the Stroop and 1450 (467 uninfected and 983 infected) completed the symbol digit test and trail making tests (TMT). We assembled a dataset consisting of participants who completed all 4 neuropsychological tests and had complete information available concerning depression score, education level, HCV RNA level, and ethnicity – 1338 women met these criteria. For participants who took these tests on multiple occasions, their first score was used for these analyses.

Statistical analysis—Distributions of Trails A and B and Stroop score were skewed slightly positively. Fourteen subjects received a score of 240 seconds on the Stroop; another 9 had scores ranging from 246 to 381 seconds – none were censored. On Trails B, 21 subjects received scores of 300 seconds; these participants were also not censored.

We compared normally distributed variables with ANOVA and determined post-hoc significance with the Games-Howell test (for unequal variances). In univariate analyses, we compared the frequency of neuropsychological impairment for each neuropsychological test as well as for summary measures across the 6 participant groups. Significance was calculated with the chi-square test. We compared data that was not normally distributed with the Kruskal-Wallis test.

We utilized general linear models to assess the significance of the HCV RNA factor and HIV/AIDS factor with either individual neuropsychological score and included 7 factors: 1) HIV group (HIV-seronegative, HIV-seropositive without AIDS, and AIDS); 2) Detectable HCV RNA (present/absent); 3) Depression group (CES-D score ≥ 23); 4) ethnicity (white, Hispanic, African-American, and other); 5) age quintile, 6) educational group, and 7) reading ability. After these factors were entered in regression models as a block, we individually assessed the possible additional contribution of HIV-related variables (CD4 count, CD4 nadir, and months on HAART), liver related variables (FIB4 and APRI), and substance abuse related (recent or past use of cocaine or heroin or excessive alcohol use).

To assess whether liver disease was associated with cognitive score, we performed separate univariate and multivariate modeling. Level of significance was set at $p < .05$, and we did not correct for multiple comparisons.

RESULTS

Demographic and clinical characteristics of the 6 patient groups defined by 3 HIV groups (not infected, HIV-seropositive but not AIDS, and AIDS) and 2 HCV groups (HCV viremic or not HCV) are shown in table 1. Participants who were HCV positive were 9 years older than HCV RNA negative subjects ($F = 38$, $p < 0.001$). Eighty-five percent of HCV-viremic participants had used intravenous drugs before recruitment into WIHS, compared to 12% of those without HCV-viremia. Only 2 participants who had not used intravenous drugs prior to enrolling into WIHS started intravenous drug use during the study.

HCV viral load did not differ among the 3 groups of participants with active HCV infection. As expected markers of liver disease, FIB-4 and APRI, were significantly higher in the HCV viremic participants. Heroin use in the 6 months prior to evaluation (already at least 5 years into recruitment into WIHS) was 14% in HCV viremic without HIV and 10% in HCV

viremic with AIDS. Heroin use in the previous 6 months in the other 4 groups was only 1–2%. Cocaine use in the previous 6 months was also more prevalent in the HCV viremic group (17.8%) than in the HCV negative group (6.9%, chi square = 27.7, $p < 0.001$).

Nadir CD4 count was lowest in the 2 AIDS groups. The two groups with AIDS had been maintained on HAART longer than those with HIV, but not AIDS. The HIV but not AIDS/HCV negative group had higher current CD4 counts than the other 3 HIV groups. HIV viral load did not differ among the 4 HIV-infected groups.

Neuropsychological Results

In multivariate models, HCV viremia was not associated with any of the cognitive outcomes (table 2). We assessed the effects of other possible confounders on cognitive score after adjusting for age quintile, ethnicity, education, reading ability, depression group, HIV group, and HCV viremia. Possible confounders such as HAART use, recent or past drug use, or serious psychiatric illness as measured by psychiatric hospitalizations did not contribute significantly to the models.

We also explored the association of FIB-4 with neuropsychological tests. In univariate analyses, FIB-4 score was associated with scores on all 4 neuropsychological tests: Stroop, Trails A, Trails B, and SDMT with correlation coefficients of 0.15, 0.12, 0.17, and -0.16 , and N s from 1269 to 1301; all significant at $p < 0.001$. In multivariate modeling using FIB-4 score, no significant associations were found.

Finally, as shown in table 2, HIV group was associated with scores on the Stroop interference test and the SDMT, but not on either Trails A or B.

DISCUSSION

To our knowledge this cohort for the study is over twice as large as any previously reported study of the effects of HCV and HIV on cognition. Only about 20% of the participants in the largest two previous studies [2,28] were women. Thus our sample includes almost 13 times as many women as any previously reported. In addition to the large size of our sample, other strengths include detailed information on liver function and drug history and our multivariate analyses controlling for confounding variables. Standardized data collection protocols with extensive training of interviewers are other strengths. Weaknesses include our limited neuropsychological battery and the relatively small size of HCV monoinfected persons. Another weakness is that although WIHS is a longitudinal study, virtually all HIV or HCV-seropositive participants were seropositive at the time of recruitment rather than acquiring infection during follow-up somewhat limiting the generalizability of our findings.

In considering the effects of HCV and HIV on cognition, 3 fundamental questions need to be asked: 1) Does HCV impair cognitive function via a mechanism independent of hepatic encephalopathy and/or depression or some other co-morbid factor? 2) Does dual infection with HIV and HCV have worse effects on cognition than HIV alone? 3) Are there plausible biological mechanisms to explain how HCV might impair cognitive function?

Because of the many factors that influence cognition, in our literature review, we focused on multivariate analyses that attempted to control for severity of liver disease. We were able to identify only 7 previous multivariate studies [2, 12, 28–32] of the effects of HCV with or without HIV on cognition that met these criteria. In one other study [10], exploratory multivariate modeling was performed. Of these, 6 [12, 28–32] included an uninfected control group and 2 [2,10] did not. Three multivariate studies with a negative-negative control group [12,30,31] found no effect for HCV in fully controlled models and three other

studies [28,29,31] found a significant effect. However, two of three positive studies [28,32] used basically the same cohort and almost half of the cohort was methamphetamine dependent. In the other study [29] details concerning multivariate analysis and the negative-negative control group were lacking.

The multivariate studies that compared HIV-monoinfected to doubly infected participants were both led by Clifford [2, 10]. The first study with only 30 doubly infected patients found that co-infected did worse than monoinfected on the DSMT. In a subsequent study, involving 172 dual infected subjects and 345 HIV-monoinfected participants, no significant differences were found.

Only women were included in our study. Men outnumbered women in virtually all previous studies. Is it possible that there is a sex specific effect where HCV affects cognition more in one sex than in another? Effects of sex on prevalence have been demonstrated in Alzheimer's disease and Parkinson's disease [33]. Some have suggested that women are more likely to be cognitively impaired in HIV [13]. To determine whether there is a sex-specific effect on cognition in HCV will require a large sample of men and women.

We recognize that several reports have suggested plausible mechanisms for HCV infection to cause cognitive impairment. HCV RNA has been demonstrated in brain [7,26]; including replicative forms within CD68 cells [5]. Patients with HCV had higher brain levels of monocyte chemotactic protein 1, TNF-alpha, and soluble TNF-receptor II than control groups [28]. We believe that potential mechanisms by which HCV could directly influence cognitive function have been identified, but a dose-response relationship between these changes and the magnitude of change in cognitive function has not yet been demonstrated.

In conclusion, we were unable to show a significant association between the presence of HCV RNA and performance on our cognitive battery nor that there is an interaction between HIV and HCV in their effect on cognitive function. Our literature review suggests that an effect of HCV on cognition that is independent of liver dysfunction has not been convincingly demonstrated. The question of whether HCV has a direct effect on cognition will require future studies with a complete neuropsychological battery, a large control group and a large group of HCV-monoinfected subjects, use of both impairment scores and mean scores on neuropsychological tests, complete data on liver function and other cofactors, and a cohort that includes both men and women.

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Table 1

Characteristics of 6 clinical groups. Values represent either mean (with standard deviation) for normally distributed continuous variables, median and quartile scores for non-normally distributed continuous variables, and frequency percentages for categorical variables.

	Group 1 HIV neg, HCV RNA neg (N = 392)	Group 2 HIV neg, HCV RNA pos (N = 42)	Group 3 HIV+, not HCV RNA neg (N = 480)	Group 4, HIV+, not AIDS, HCV RNA pos (N = 96)	Group 5 AIDS, HCV RNA neg (N = 241)	Group 6 AIDS, HCV RNA pos (N = 88)	P, significant comparisons
Age	36.1 (9.8)	45.9 (8.2)	38.3 (8.8)	47.8 (6.3)	43.2 (7.8)	48.3 (5.1)	1 v 2 ^{!!} , 3 [*] , 5 [*] , 6 [*] 3 v 6 [*] 5 v 6 [*]
Ethnicity	9.4% W 22.7% Hisp 63.8% AA 4.1% Other	11.9 W 21.4 Hisp 64.3 AA 2.4 Other	9.6 W 16.9 Hisp 70.0 AA 3.5 Other	15.6 W 14.6 Hisp 69.8 AA 0 Other	19.1 W 19.1 Hisp 57.3 AA 4.6 Other	10.2 W 22.7 Hisp 64.8 AA 2.3 Other	$\chi^2=31.1$, 0.008
Education Level	1: 30.6% 2: 31.4% 3: 29.6% 4: 8.4%	1: 52.4% 2: 38.1% 3: 9.5% 4: 0%	1: 30.6% 2: 31.7% 3: 28.5% 4: 9.2%	1: 39.6% 2: 31.3% 3: 24.0% 4: 5.2%	1: 29.5% 2: 37.8% 3: 25.7% 4: 7.1%	1: 39.8% 2: 29.5% 3: 25.0% 4: 5.7%	$\chi^2=25.5$, 0.04
Percent with CES-D ≥ 23	14.0	23.8%	11.7%	11.5%	11.6%	15.9%	$\chi^2=6.7$, 0.24
CD4 count	1061(474)	1204 (603)	531 (273)	454 (264)	423 (272)	425(288)	3 v 5 [*] , 6 ^{!!}
CD4 nadir	771 (283)	809 (394)	301 (187)	259 (195)	183 (159)	195 (145)	3 v 5 [*] , 6 [*] 4 v 5 ^{!!}
Months on HAART	0 (0)	0 (0)	53.6 (35.6)	58.0 (39.3)	71.3 (33.4)	64.2 (36.6)	3 v 5 [*] 4 v 5 [!]
HCV RNA levels		0.67 M (0.28-3.46)		1.59 M (0.65 M – 3.29 M)		1.91 M (0.44-4.7 M)	All NS
HIV levels			98 (< 80, 4400)	92 (< 80, 3200)	<80 (<80, 6500)	260 (< 80, 4700)	All NS
FTB-4	0.64(0.69)	1.79 (1.84)	0.89 (0.58)	2.76 (7.4)	1.20 (0.93)	2.20 (1.36)	1 v 2 ^{!!} , 3 [*] , 5 [*] , 6 [*] 2 v 3 [!] 3 v 5 [*] , 6 [*] 5 v 6 [*]
APRI	0.19 (0.18)	0.73(0.95)	0.28 (0.24)	1.12(3.98)	0.34 (0.28)	0.72 (0.57)	1 v 2 ^{!!} , 3 [*] , 5 [*] , 6 [*] 3 v 6 [*] 5 v 6 [*]

	Group 1 HIV neg, HCV RNA neg (N = 392)	Group 2 HIV neg, HCV RNA pos (N = 42)	Group 3 HIV+, not AIDS, HCV RNA neg (N = 480)	Group 4, HIV+, not AIDS, HCV RNA pos (N = 96)	Group 5 AIDS, HCV RNA neg N= 241	Group 6 AIDS, HCV RNA pos (N = 88)	P, significant comparisons
Percent Baseline intravenous drug users	10.5%	78.6%	9.2%	82.3%	18.3%	89.8%	$\chi^2 = 559, p < .001$
Percent using Heroin in past 6 months	2%	14%	1%	2%	2%	10%	$\chi^2 = 45.9, < .0001$
Percent using cocaine in last 6 months	9.4%	23.8%	4.6%	13.7%	7.5%	19.3%	$\chi^2 = 38.3, < .0001$
Percent reporting > 14 drinks/wk	6.7%	9.5%	2.3%	5.3%	4.6%	11.6%	$\chi^2 = 19.1, 0.002$
Stroop	124 (30)	139 (36)	126 (34)	141 (40)	137 (37)	144 (47)	1 v 4 ^{!!} , 5 [*] , 6 ^{!!} 3 v 4 ^{!!} , 5 ^{!!} , 6 ^{!!}
SDMT	45.2 (11.8)	37.8 (10.3)	43.3 (12.6)	39.5 (11.6)	42.0 (12.1)	36.4 (12.2)	1 v 2 ^{!!} , 4 [*] , 5 ^{!!} , 6 [*] 2 v 3 ^{!!} 3 v 6 [*] 5 v 6 ^{!!}
Trails A	36.0 (13.8)	43.1 (18.0)	39.2 (16.6)	43.8 (21.7)	39.1 (23.5)	44.8 (22.1)	1 v 3 ^{!!} , 4 ^{!!} , 6 ^{!!}
Trails B	85.1 (41.5)	128.9 (77.6)	89.8 (43.8)	104.3 (59.0)	95.6 (56.6)	114.1 (60.9)	1 v 2 ^{!!} , 4 ^{!!} , 6 ^{!!} 2 v 3 ^{!!} 3 v 6 ^{!!}

* <0.001,

[!] 0.01 ≤ p < 0.05,

^{!!} 0.001 ≤ p < 0.01.

SDMT – symbol digit (modalities) test. See methods for description of education levels.

Table 2

General linear models for predicting listed outcomes. N = 1076. Models also include age-quintile, education group, ethnicity, depression group, and reading ability. Other variables explored but not kept in the models included cocaine-use, heroin-use, excess alcohol use, major psychiatric illness, CD4 nadir, CD4 number, months on HAART, APRI, and FIB4.

Dependent (outcome) variable	Independent (predictor) variable	F, p
Stroop (N = 1098, R ² = 0.19)	Intercept	1218, <0.001
	HIV Group	6.2, 0.002
	HCV RNA positive	0.9, 0.35
SDMT (N = 1064, R ² = 0.28)	Intercept	366, <0.001
	HIV Group	1.5, 0.22
	HCV RNA positive	0.22, 0.64
Trails A (N = 1058; R ² = 0.12)	Intercept	663, <0.001
	HIV Group	1.3, 0.26
	HCV RNA positive	0.5, 0.49
Trails B (N = 1045; R ² = 0.20)	Intercept	429, <0.001
	HIV Group	0.7, 0.49
	HCV RNA positive	3.6, 0.06