

Neuropsychological Impairment in Patients With Chronic Hepatitis C

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Hepatitis C is the most common cause of chronic liver disease in the United States and it significantly reduces quality of life. The role of cognitive deficits contributing to the morbidity of this disease has not been well characterized. The purpose of this study was to examine cognitive functioning in patients with chronic hepatitis C and to investigate relationships among parameters of disease severity and performance on neuropsychological tests. Sixty-six patients with chronic hepatitis C and 14 patients with other chronic liver diseases were administered a brief battery of neuropsychological tests assessing attention, visuoconstructional ability, learning, memory, and psychomotor speed. Cognitive impairment in patients with chronic hepatitis C ranged from 0% on a visuoconstructional task to 82% on a measure of sustained attention and concentration. Test scores of patients with chronic hepatitis C did not differ from those of patients with other chronic liver diseases. Hence, patients with and without chronic hepatitis C experience cognitive deficits, especially in tasks requiring attention and psychomotor speed. In addition, there was a significant relationship between fibrosis stage and test performance, with greater fibrosis associated with poorer performance. However, both patients with and without cirrhosis exhibited cognitive dysfunction. In conclusion, these findings suggest that progressive hepatic injury may result in cognitive problems even before the development of cirrhosis. Future studies need to determine the effect of this decrease in cognitive function on quality of life. (HEPATOLOGY 2002;35:440-446.)

The hepatitis C virus (HCV) is the most common cause of chronic liver disease in the United States and the leading indication for liver transplantation.¹ According to a population-based study conducted from 1988 to 1994, an estimated 2.7 million individuals are currently infected with HCV.² The proportion of HCV-infected patients with cirrhosis is expected to increase from the 15.6% noted in 1988 to an estimated 28.9% by 2018.³ Increases of 84% and 63% are expected in the rates of hepatic decompensation and hepatocellular carcinoma, respectively, and deaths related to HCV are expected to triple over the next 2 decades.³

Multiple studies have revealed that infection with HCV significantly reduces quality of life (QOL), even in the absence of cirrhosis.^{4,5} Currently, there is no clear explanation for this reduction. Koff⁶ suggested that pathophysiological events resulting from infection may be contributing to decreased QOL in HCV-infected patients. This decrease may be related to the impact of HCV infection on cognitive abilities, such as attention and memory func-

tioning. In patients with cirrhosis and end-stage liver disease, neuropsychological impairment has been well documented.^{7,8} These deficits have been attributed to molecules and toxins accumulating in the blood that are not effectively cleared by the cirrhotic liver. In patients with HCV infection, it often takes more than 20 years of chronic hepatic injury before the liver develops cirrhosis and its complications. During this time, liver function is impaired, albeit slightly. The possibility that cognitive dysfunction may result from slight impairment of liver function, even before the development of cirrhosis, has not been well examined, nor has the possibility that infection with HCV itself may result in cognitive impairment.

There were 2 primary purposes of this study. First, we investigated the prevalence of cognitive impairment of patients with HCV. We then compared test performances of HCV-infected patients to those of patients with other types of chronic liver diseases to explore whether infection with HCV was associated with greater cognitive dysfunction. We hypothesized that patients with HCV would perform significantly worse on tests of cognitive functioning than patients with other types of chronic liver disease because of reports of decreased QOL in patients with HCV compared with patients with other types of chronic liver disease.^{4,9} Second, we examined the relationship between fibrosis stage and test performance to ascertain the association between disease severity and cognitive dysfunction. Our hypothesis was that greater fibrosis would be associated with poorer test performance. We also explored the prevalence of impaired neuropsychological performances of noncirrhotic patients to determine if cognitive deficits exist in the absence of advanced liver injury (*i.e.*, cirrhosis) and then compared performances of noncirrhotic patients with those of cirrhotic patients. We hypothesized that noncirrhotic patients

Abbreviations: HCV, hepatitis C virus; QOL, quality of life; HIV, human immunodeficiency virus; TMT, trail making test; SDMT, symbol digit modalities test.

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would perform better than cirrhotic patients on all neuropsychological measures.

Patients and Methods

Sample

All patients with chronic liver disease who attended an adult outpatient clinic at the University of California, San Diego Liver Center from September 1999 through June 2000 and who were able to read and understand English were eligible for this study. Of all eligible patients, 269 were randomly selected and asked to participate in a study examining the impact of chronic liver disease on QOL. Of the 269 patients approached, 15 (5%) refused participation. The remaining 254 patients agreed to participate and provided written informed consent as approved by the Institutional Review Board at University of California, San Diego. Out of these 254 patients, 140 (55%) completed and returned the initial set of study questionnaires, making them eligible for the second phase of the study—neuropsychological testing during their next clinic visit. Patients who did not complete and return study questionnaires ($N = 114$) did not differ in age [$t(251) = 0.05$], gender [$\chi^2(1) = 0.04$], ethnicity [$\chi^2(2) = 2.92$], etiology of liver disease [$\chi^2(2) = 2.66$], or cirrhosis [$\chi^2(1) = 3.58$] from patients who completed and returned the questionnaires. Group differences in education level, if present, could not be determined because this information was not consistently available in the medical record.

Because of scheduling conflicts and attrition, only 86 of the 140 participants eligible for the second phase of the study completed neuropsychological testing. Data from 6 of these participants were excluded from further analyses because they were post-liver transplant patients and were no longer considered to have chronic liver disease. Therefore, data from 80 patients were retained for the remaining analyses. Excluded patients and patients unable to complete neuropsychological testing ($N = 54$) did not differ significantly from the final sample in age [$t(138) = -.01$], education [$t(133) = .67$], gender [$\chi^2(1) = .51$], ethnicity [$\chi^2(2) = .19$], etiology of liver disease [$\chi^2(2) = .07$], or fibrosis stage [$\chi^2(4) = 1.76$].

Average age of the final sample was 45.98 years ($SD = 8.55$), and average education was 13.31 years ($SD = 2.33$). The majority of patients were male (64%), and most were White (68%). Average estimated IQ as measured by the Shipley Institute of Living Scale¹⁰ was 102.68 ($SD = 13.53$), which is in the average range. QOL was measured with the SF-36,¹¹ and level of fatigue was assessed using the Fatigue Severity Scale.¹² The average SF-36 Physical and Mental Composite Scores (PCS and MCS) for this sample were 37.86 ($SD = 11.92$) and 42.95 ($SD = 11.05$), respectively. Average level of fatigue was 4.44 ($SD = 1.7$) on a scale from "1" (*i.e.*, least severe) to "7" (*i.e.*, most severe). Twenty-seven percent of patients were taking psychiatric medication at the time of the study, and 48% reported they had taken psychiatric medication in the past. These percentages are very similar to those reported by Dwight et al.,¹³ who found that 28% of their sample were currently depressed and 44% had lifetime histories of major depression or dysthymia. Most of the current sample (67%) admitted to a history of illicit drug abuse, with 3 patients reporting drug abuse in the past month. The majority of patients, 69%, denied current alcohol use, with another 27% reporting alcohol use less than once a month. Thus,

only 4% of the sample reported alcohol use more than 2 to 4 times a month.

Sixty-six of the 80 patients were diagnosed with chronic HCV, and 14 were diagnosed with other etiologies of liver disease. Forty-four of the 66 HCV-infected patients had no medical problems other than HCV. The remaining 22 were diagnosed with the following comorbid chronic conditions: alcoholic hepatitis ($N = 10$), human immunodeficiency virus (HIV; $N = 8$), hepatitis B ($N = 2$), alcoholic hepatitis and hepatitis B ($N = 1$), and a small liver tumor ($N = 1$). Diagnoses of the 14 patients with chronic liver diseases other than HCV included hepatitis B ($N = 5$), cryptogenic ($N = 4$), alcoholic hepatitis ($N = 2$), autoimmune hepatitis ($N = 2$), and nonalcoholic fatty liver ($N = 1$). Of the 66 HCV-infected patients, 24% had been previously treated with interferon therapy and 23% were undergoing interferon therapy at the time of the study.

Fibrosis stage was determined by liver biopsy according to the METAVIR scoring system.¹⁴ Level of fibrosis was graded as none in 9 patients, stage 1 (mild) in 15 patients, stage 2 (moderate) in 4 patients, and stage 3 (severe) in 13 patients. Stage 4 (cirrhosis) was identified in 34 patients. Liver biopsy was not performed on 5 patients for the following reasons: severe psychiatric problems ($N = 1$), hemophilia ($N = 1$), biopsy at another institution within the past 3 years ($N = 1$), refusal ($N = 1$), and failure to return for biopsy ($N = 1$). Diagnoses of the 5 patients who were not biopsied were HCV ($N = 3$), HCV and alcoholic hepatitis ($N = 1$), and HCV and HIV ($N = 1$). No patient was suffering from delirium or clinically evident hepatic encephalopathy at the time of the study.

Measures

Selection of neuropsychological tests was based primarily on the necessity for assessment of relevant cognitive functions in a short amount of time. Because the most consistently reported cognitive impairments in cirrhotic patients have been attention problems and psychomotor dysfunction,^{7,8} the test battery was more heavily weighted with measures used to detect these problems. Assessment of learning and memory was also deemed important given the potentially adverse impact of these impairments on daily functioning and QOL. Additional criteria for inclusion in the test battery were: (1) good psychometric properties, (2) availability of demographically corrected norms, (3) brevity and ease of scoring and administration, (4) prior use with chronic liver disease patients, and (5) sensitivity to the effects of brain dysfunction. All measures were administered and scored according to standardized instructions. Scores more than 1 SD below the normative mean were considered impaired, as this criterion is often considered clinically meaningful when using demographically corrected norms.

Key Complex Figure Test (modified version).¹⁵ Patients are presented with a complex figure and required to copy it. Immediately following completion of the copy trial, the figure is removed and patients are asked to reproduce the figure from memory. Patients unable to remember at least 60% of the figure on this trial are allowed a second learning trial where they are shown the figure for 10 seconds and then asked to reproduce the figure from memory. A third learning trial is administered to patients who again fail to remember at least 60% of the figure. Approximately 20 minutes after the last exposure to the figure, patients are asked to reproduce the figure from memory. Three scores are derived from this test: (1)

the copy score, (2) the learning score, and (3) percent forgotten following the 20-minute delay. This modified version of the Rey Complex Figure test provides information about learning, memory, and visuoconstructional abilities. Age-corrected norms are used to determine impairment.

Digit Cancellation.¹⁵ This task consists of an $8\frac{1}{2} \times 11$ inch page with 28 rows of 36 digits each. The patient is asked to cross out all of the 3s as quickly as possible. The total time taken (in seconds) and the number of errors of omission and commission are recorded. Digit Cancellation is considered a test of sustained attention and concentration. Impairment is determined by comparing patients' scores to an age-matched normative group.

Trail Making Test (TMT).¹⁶ The TMT assesses psychomotor speed, visual scanning and tracking, attention and concentration, and sequencing. There are 2 parts to this test, Parts A and B. On Part A, patients are asked to serially connect digits that have been scattered on a page as quickly as possible. On Part B, patients are asked to sequentially alternate numbers and letters (*i.e.*, 1 - A - 2 - B - 3 - C, etc.) as quickly as possible. Time taken (in seconds) to complete each part is recorded, and impairment is determined by comparing patients' performances to age- and education-matched normative samples.

Symbol Digit Modalities Test (SDMT).¹⁷ The SDMT provides a measure of attention, complex scanning, visual tracking, and psychomotor speed. On this test, patients are provided a legend of 9 corresponding symbols and numbers at the top of a page. Below the legend are rows of symbols without their corresponding numbers. Patients are asked to write the corresponding number beneath each symbol as quickly as possible. The number of correct responses in 90 seconds is the final score. Age- and education-matched norms are used to determine impairment.

Data Analysis

Based on our study goal of examining differences in neuropsychological test performances between patients with HCV and patients with other etiologies of liver disease, the sample of 80 patients was divided accordingly ($N = 66$ and 14 , respectively). Because our hypothesis was directional (*i.e.*, that HCV-infected patients would perform significantly worse than patients not infected with HCV), and we were expecting a large effect size (*i.e.*, $.80$), a minimum of 12 patients per group was necessary to detect a significant group difference using the recommended 4:1 ratio of β to α (*i.e.*, $\alpha = .05$).¹⁸

As noted above, 22 patients in the HCV group suffered comorbid chronic conditions, which may increase the likelihood of cognitive dysfunction. Therefore, we examined the appropriateness of considering these patients separately from patients with HCV and no other medical problems. To achieve this, we used independent samples *t*-tests for neuropsychological test scores (adjusting for unequal variances where indicated) and χ^2 analysis for level of fibrosis. In addition, analyses of group differences in variables that might influence interpretation of neuropsychological test performance (*i.e.*, age, education, estimated IQ, QOL, fatigue, psychiatric medication usage, substance use, and treatment with interferon) were performed. Alpha was set at $.05$ for all preliminary analyses to increase the likelihood of finding significant differences that may impact interpretation of subsequent results.

Basic descriptive statistics, including frequency distributions and cross-tabulations, were used to characterize neuropsychological performances and associated impairment. χ^2 analyses were conducted to examine significant group differences in proportion to impaired test performances. To decrease the likelihood of a Type II error, a Bonferroni correction for multiple comparisons was applied, resulting in an α level of $.006$ (*i.e.*, $.05/8$) as indicative of statistical significance. Multivariate analysis was employed to examine group differences in neuropsychological test scores.

Spearman correlations were computed to determine the association between fibrosis stage and neuropsychological test performance. One-tailed significance levels were employed given our directional hypothesis that greater fibrosis would be associated with poorer test performance. To investigate whether or not non-cirrhotic and cirrhotic patients differed in demographic characteristics that might influence neuropsychological test interpretation, independent samples *t*-tests were used. Hotelling's *T* was utilized to compare neuropsychological test performances between these 2 groups, and χ^2 analyses were used to explore whether significant differences existed in the proportion of impaired performances. As before, a Bonferroni correction was utilized for the multiple χ^2 analyses, resulting in an α level of $.006$ needed for statistical significance. Because our hypothesis was directional (*i.e.*, that non-cirrhotic patients would perform better than cirrhotic patients), one-tailed tests were utilized.

Results

Significant differences were found between patients with HCV only and patients with HCV plus another chronic medical condition on 4 of the 8 neuropsychological measures: (1) digit cancellation time [$t(59) = -2.00$; $P = .05$], (2) TMT Part A [$t(64) = -2.37$; $P = .02$], (3) TMT Part B [$t(64) = -2.71$; $P = .01$], and (4) SDMT [$t(64) = 3.00$; $P = .004$]. On all 4 measures, HCV patients with comorbid medical conditions performed significantly worse than patients with HCV only. Additionally, these 2 HCV patient groups differed significantly in level of fibrosis [$\chi^2(4) = 12.30$; $P = .02$]; patients with HCV plus another chronic condition had significantly worse fibrosis. HCV-infected patients with comorbid alcoholic hepatitis ($N = 10$) did not differ significantly from HCV-infected patients with other comorbidities ($N = 12$) on any of the neuropsychological measures [$t(20)$ ranged from -0.15 to 1.63]. Likewise, patients co-infected with HCV and HIV ($N = 8$) did not differ significantly from patients with HCV plus other comorbidities ($N = 14$) on any of the neuropsychological measures [$t(20)$ ranged from 0.47 to -1.90]. However, HCV-infected patients with alcoholic hepatitis were significantly more likely to have cirrhosis than HCV-infected patients with other types of chronic medical conditions [$\chi^2(1) = 5.46$; $P = .02$], and HCV/HIV patients were significantly less likely to have cirrhosis than HCV-infected patients with other comorbidities [$\chi^2(1) = 12.38$; $P < .001$].

Based on the above results, the 2 HCV groups were kept separate for the remaining analyses. Thus, patients with HCV and no other medical problems comprised Group 1 ($N = 44$), patients with HCV plus comorbid medical conditions comprised Group 2 ($N = 22$), and patients with other etiologies of liver disease comprised Group 3 ($N = 14$). No significant differences in age, edu-

cation, or estimated IQ were found among the 3 liver disease groups [$F(2) = .04, 1.31, \text{ and } 2.48$, respectively], and multivariate analysis of variance failed to reveal significant group differences in SF-36 PCS, MCS, and FSS scores [$F(6) = 1.59$]. In addition, the proportion of patients with past or current psychiatric medication usage did not differ significantly among the 3 groups [$\chi^2(2) = .11$ and $.92$, respectively], and neither did the proportion of patients with a history of illicit drug abuse or current alcohol use [$\chi^2(2) = 2.49$ and 1.92 , respectively]. Further, the percentage of HCV patients with and without comorbid medical problems did not differ significantly with regard to past (18% vs. 27%, respectively) or current (27% vs. 20%, respectively) treatment with interferon [$\chi^2(1) = .66$ and 0.39 , respectively].

Neuropsychological Impairment of HCV-Infected Patients

Percentages of impaired neuropsychological performances by group are shown in Table 1. Cognitive impairment in Group 1 ranged from 0% on the Rey Complex Figure copy trial to 49% on Digit Cancellation time. In Group 2, impaired performances ranged from 9% on the Rey Complex Figure copy trial to 82% on Digit Cancellation time. Impairment in Group 3 ranged from 0% on the Rey Complex Figure copy trial to 39% on Digit Cancellation time. When impairment was present on a measure, it ranged from mild to severe (i.e., $\leq 5^{\text{th}}$ percentile) in all patient groups. Using χ^2 analyses, there were significant group differences in percentage of impaired performance on Digit Cancellation time and SDMT [$\chi^2(2) = 8.48$ and 10.34 ; $P = .005$ and $.003$, respectively]. Follow-up analyses showed that significantly more patients in Group 2 exhibited impaired performances than patients in Groups 1 and 3 on both Digit Cancellation time (82% vs. 49% and 39%, respectively) and SDMT (59% vs. 25% and 14%, respectively). Groups 1 and 3 did not differ significantly from each other on either measure.

Means and standard deviations of neuropsychological test scores for all three groups are presented in Table 2. The data in Table 2 revealed a trend in which patients without chronic HCV performed better than patients with chronic HCV, and patients with chronic HCV plus another chronic medical condition performed worst of all. This trend was evident on all measures except the Rey Complex Figure percent forgotten. However, results of the

Table 1. Percentage of Impaired Neuropsychological Test Performances by Group

Measure	Group 1 (N = 44)	Group 2 (N = 22)	Group 3 (N = 14)	P
RCF Copy	0%	9%	0%	.037
RCF Learning	21%	46%	15%	.035
RCF % Forgotten	14%	23%	15%	.331
DC Time	49%	82%*	39%	.005
DC Errors	21%	36%	15%	.139
TMT-Part A	25%	41%	21%	.162
TMT-Part B	21%	41%	29%	.107
SDMT	25%	59%*	14%	.003

NOTE. Group 1 = hepatitis C only; Group 2 = hepatitis C plus another chronic illness; Group 3 = other chronic liver diseases.

Abbreviations: RCF, Rey Complex Figure; DC, Digit Cancellation; TMT, Trail Making Test; SDMT, Symbol Digit Modalities Test.

*Significantly different from Groups 1 and 3.

Table 2. Means (Standard Deviations) of Neuropsychological Test Scores by Group

Measure	Group 1 (N = 44)	Group 2 (N = 22)	Group 3 (N = 14)
RCF Copy	18.5 (1.3)	17.4 (4.0)	19.3 (1.2)
RCF Learning	13.5 (5.1)	11.1 (6.1)	14.0 (4.1)
RCF % Forgotten	3.1 (15.5)	5.6 (20.0)	7.5 (16.3)
DC Time (secs)	193.3 (55.4)	219.3 (45.9)	180.5 (56.3)
DC Errors	6.1 (6.3)	7.9 (8.2)	3.4 (4.3)
TMT-A (secs)	32.1 (13.1)	38.6 (15.1)	27.8 (9.6)
TMT-B (secs)	77.4 (43.8)	105.9 (59.1)	65.3 (24.1)
SDMT	45.5 (8.6)	39.5 (12.5)	50.1 (5.1)

NOTE. Group 1 = hepatitis C only; Group 2 = hepatitis C plus another chronic illness; Group 3 = other chronic liver diseases.

Abbreviations: RCF, Rey Complex Figure; DC, Digit Cancellation; TMT, Trail Making Test; SDMT, Symbol Digit Modalities Test.

MANOVA failed to reveal significant group differences in the actual neuropsychological test scores [$F(16) = 1.00$; $P = .47$].

Relationships Between Disease Severity and Neuropsychological Performance

There were significant associations in the hypothesized direction between stage of fibrosis and cognitive performance on 4 of the 8 neuropsychological measures: Digit Cancellation time, Parts A and B of the TMT, and SDMT. In all cases, greater fibrosis was associated with poorer neuropsychological performance. Correlation coefficients ranged from $.27$ on Part B of the TMT to $.43$ on Part A of the TMT (see Table 3).

The prevalence of impaired neuropsychological test performances in patients without cirrhosis ranged from 0% on Rey Complex Figure copy trial to 50% on Digit Cancellation time, and the prevalence of impaired neuropsychological test performances of patients with cirrhosis ranged from 6% on the Rey Complex Figure copy trial to 60% on Digit Cancellation time (see Table 4). Although a greater proportion of cirrhotic patients performed in the impaired range on all measures except Rey Complex Figure learning, significant group differences in proportion of impaired performances were found on only one measure, the SDMT [$\chi^2(1) = 4.99$; $P = .005$]. Forty-four percent of patients with cirrhosis performed in the impaired range on SDMT compared with 20% of patients without cirrhosis.

No significant differences in education or estimated IQ were found between patients with and without cirrhosis [$t(70) = 1.44$

Table 3. Relationships Between Level of Fibrosis and Neuropsychological Test Performances by Measure (N = 80)

Measure	r	P
RCF Copy	-.08	.25
RCF Learning	-.01	.46
RCF % Forgotten	.03	.39
DC Time	.31	.005
DC Errors	-.04	.38
TMT-A	.43	<.001
TMT-B	.27	.009
SDMT	-.41	<.001

Abbreviations: RCF, Rey Complex Figure; DC, Digit Cancellation; TMT, Trail Making Test; SDMT, Symbol Digit Modalities Test.

Table 4. Percentage of Impaired Neuropsychological Test Performances in Noncirrhotic and Cirrhotic Patients by Measure

Measure	Noncirrhotics (N = 40)	Cirrhotics (N = 34)	P*
RCF Copy	0%	6%	.060
RCF Learning	28%	24%	.352
RCF % Forgotten	15%	18%	.376
DC Time	50%	61%	.214
DC Errors	29%	18%	.110
TMT-A	23%	35%	.112
TMT-B	20%	32%	.113
SDMT	20%	44%	.005

Abbreviations: RCF, Rey Complex Figure; DC, Digit Cancellation; TMT, Trail Making Test; SDMT, Symbol Digit Modalities Test.

*One-tailed significance.

and -1.25 , respectively]; however, there was a significant group difference in age [$t(72) = -2.18$; $P = .03$]. Noncirrhotic patients were significantly younger than cirrhotic patients (*i.e.*, 44.53 years and 48.79 years, respectively). Thus, age was entered as a covariate in subsequent analyses. There were no significant differences between cirrhotic and noncirrhotic patients in SF-36 PCS, MCS, and FSS using the multivariate t -test or Hotelling's T [$T^2 = .06$, associated $F(3) = 1.29$], and the 2 groups did not differ in the proportion of patients with current or past psychiatric medication usage, history of drug abuse, and current alcohol use [$\chi^2(1) = .39$, 2.20, .74, and 3.62, respectively]. With regard to neuropsychological test performance, using age as a covariate, Hotelling's T was significant [$T^2 = .39$, associated $F(8) = 2.76$; $P = .01$], with group differences found on Digit Cancellation time and Part A of the TMT. On both measures, cirrhotic patients performed significantly worse than noncirrhotic patients (see Table 5).

Given the significant differences in test scores between noncirrhotic and cirrhotic patients, we investigated whether or not the presence of cirrhosis impacted our ability to identify significant differences in test performances among liver disease groups (*i.e.*, Groups 1-3). We examined neuropsychological test performances of noncirrhotic patients only. Because Group 2 contained only 5 noncirrhotic patients, we combined Groups 1 and 2 to form one HCV group ($N = 34$) and compared their test scores with test scores of noncirrhotic patients in Group 3 ($N = 6$). Hotelling's T was not significant [$T^2 = .29$, associated $F(8) = 1.05$; $P = .42$].

Discussion

This study examined neuropsychological dysfunction in patients with chronic HCV. Results of this study revealed that a significant percentage of patients with chronic HCV experience cognitive deficits, especially in the domains of attention, learning, psychomotor speed, and mental flexibility. In contrast, visuoconstructional skills and the ability to remember previously learned information following a delay were relatively intact. This pattern of cognitive dysfunction is similar to that reported in patients with mild neurocognitive disorder associated with other chronic illness, such as HIV and AIDS-related dementia,¹⁹ and is most consistent with a subcortical pattern of deficits. The neuropsychological manifestation of subcortical deficits usually includes slowed informa-

tion processing speed, reduced word fluency, psychomotor slowing, and impaired learning in the presence of good recall of previously learned information and intact recognition memory. Verbal skills, such as vocabulary and naming, and basic visuospatial and visuoconstructional abilities are relatively unaffected.

There were no significant differences in neuropsychological test scores of patients with chronic HCV only (*i.e.*, Group 1), chronic HCV plus comorbid conditions (*i.e.*, Group 2), and other types of chronic liver disease (*i.e.*, Group 3). These results suggest that the effects of HCV on cognitive performance are not different from those associated with other causes of chronic liver disease. However, the percentage of patients with impaired performance differed by group on a measure of sustained attention and concentration (*i.e.*, Digit Cancellation time) and on a measure of attention, visual scanning and tracking, and psychomotor speed (*i.e.*, SDMT). On both measures, Group 2 showed significantly higher percentages of impaired performances than Groups 1 and 3, which did not differ significantly from each other. This finding suggests that chronic HCV in combination with comorbid chronic illness may result in increased levels of cognitive dysfunction, especially in the presence of alcoholic hepatitis. This result cannot be attributed to age, education, estimated IQ, overall QOL, fatigue, psychiatric medication usage, substance use, or treatment with interferon.

Before the identification of HCV, Tarter et al.²⁰ attempted to identify neurocognitive differences among specific types of liver disease in patients with cirrhosis. Unlike the results of the current study, Tarter et al. found significant group differences in neuropsychological performance according to the underlying liver disease. The differing results of these 2 studies may be related to sample differences in severity and stage of liver disease. It also is possible that significant differences among etiology groups were not evident in the current study because of the relatively small and heterogeneous sample of patients with other types of chronic liver disease (*i.e.*, $N = 14$). Therefore, replication of this finding using larger, more homogenous samples stratified by level of fibrosis is needed before definitively concluding that there are no HCV-specific pathophysiological effects on cognitive functioning.

This study also reports neuropsychological impairment in patients who have not yet developed cirrhosis. Impaired performances were found in up to 50% of noncirrhotic patients, depending on the neuropsychological function tested. Of the cognitive functions measured, only visuoconstructional ability was within

Table 5. Means (Standard Deviations) of Neuropsychological Test Scores by Group

Measure	Noncirrhotic (N = 40)	Cirrhotic (N = 34)
RCF Copy	18.8 (1.3)	17.8 (3.3)
RCF Learning	12.7 (5.5)	13.6 (4.4)
RCF % Forgotten	5.8 (15.3)	4.2 (17.7)
DC Time (secs)*	185.2 (55.8)	212.6 (50.4)
DC Errors	6.7 (6.8)	4.9 (6.1)
TMT-A (secs)*	29.3 (9.7)	37.8 (16.0)
TMT-B (secs)	73.5 (38.9)	90.6 (56.1)
SDMT	47.0 (8.4)	42.8 (9.6)

Abbreviations: RCF, Rey Complex Figure; DC, Digit Cancellation; TMT, Trail Making Test; SDMT, Symbol Digit Modalities Test.

* $P < .05$.

normal limits for all noncirrhotic patients. Maintaining attention and concentration for more than a couple of minutes while performing accurately (*i.e.*, Digit Cancellation) was the most difficult task for noncirrhotic patients, with 50% taking an abnormally long time to complete the task and 28.9% making a significant number of omission errors. In addition, about 20% of noncirrhotic patients performed in the impaired range on 3 other measures involving attention/concentration, visual scanning and tracking, psychomotor speed, and mental flexibility (*i.e.*, Parts A and B of the TMT and SDMT). These results suggest that attention and concentration may be the cognitive skill most affected early in the course of chronic liver disease.

Convergent evidence of impaired cognition in patients without cirrhosis has also been found using neurophysiological measures of brain functioning.²¹ On EEG, Kramer et al.²¹ showed that P300 event-related potentials of 58 noncirrhotic HCV patients were impaired compared with healthy subjects. Following treatment with antiviral therapy, EEG findings were improved in 7 of 9 patients. Thus, early identification and treatment of chronic HCV irrespective of histologic stage may improve cognitive functioning.

There were significant associations between fibrosis stage and neuropsychological test performances on 4 of 8 measures, Digit Cancellation time, Parts A and B of the TMT, and SDMT. In all cases, greater levels of fibrosis were associated with greater cognitive dysfunction. These associations suggest that the longer one experiences chronic hepatic injury, the more likely one is to develop neurocognitive problems. However, not all cognitive functions appear to be affected equally. Measures of sustained and complex attention, psychomotor speed, visual scanning and tracking, and mental flexibility were more impaired in cirrhotic patients, although group differences in actual test scores reached statistical significance for only 2 of the 4 measures (*i.e.*, Digit Cancellation time and TMT Part A), and group differences in percentage of impaired performances were found on only one measure (*i.e.*, SDMT). These findings are consistent with recent studies of cognitive impairment in patients with subclinical hepatic encephalopathy, which have suggested involvement of subcortical pathways such as the basal ganglia-thalamocortical circuit.^{8,23}

Neurocognitive problems such as these can greatly impact performance on daily activities. Problems paying attention and concentrating can interfere with one's ability to learn new information, focus on a single task for a long period of time, and/or perform multiple tasks simultaneously without error. Psychomotor slowing, especially in combination with impaired attention and concentration, can result in prolonged periods of time needed to complete even routine tasks. Patients with these types of neurocognitive problems may fail to remember (or remember incorrectly) details about their liver disease, treatment regimen, and/or physicians' recommendations. They may experience difficulty performing their household and job duties as efficiently and/or as accurately as they are accustomed to, which may lead to claims of disability. As a result of these difficulties, many patients experience frustration and mood problems, such as depression and anxiety, which often exacerbate the underlying problem.

The current findings must be interpreted within the context of the study sample. Consecutive patients were recruited from a specialty liver clinic at a large university medical center. Thus, this

patient population may not be representative of all patients with chronic liver disease. It is likely that our patient sample had more significant liver disease and/or comorbid medical problems than patients managed solely by their primary care physicians or persons in the general population with chronic liver disease. An additional limitation is the low number of initially recruited subjects that actually completed neuropsychological testing (*i.e.*, 86 out of 254); however, there were no significant group differences in age, gender, ethnicity, etiology of liver disease, and fibrosis between patients who did and did not complete neuropsychological measures.

In summary, there were no significant differences in neuropsychological test scores between HCV-infected patients and patients with other chronic liver diseases. However, a greater proportion of patients with HCV plus a comorbid illness performed in the impaired range than patients with HCV only or another type of chronic liver disease. Greater fibrosis was significantly associated with poorer cognitive functioning. Although patients with cirrhosis generally performed more poorly on neuropsychological measures than precirrhotic patients, a significant percentage of patients without cirrhosis were found to exhibit cognitive deficits. In conclusion, results of this study suggest that HCV and other chronic liver diseases adversely affect cognitive functioning, even in the absence of cirrhosis. Attention and concentration abilities appear to be affected earliest in the disease process, although problems with learning, psychomotor speed, and mental flexibility are also present to a lesser extent. These deficits, regardless of their cause, may affect QOL and performance in the work and home environments. Hence, early identification and treatment of chronic liver disease could be critical in diminishing detrimental effects on brain function. The degree of cognitive dysfunction of patients with chronic liver disease should be considered when evaluating the functional capacity of these patients.

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