

Hepatitis C virus infection and neurocognitive function

Abstract—Hepatitis C virus (HCV) infection may be associated with neurocognitive deficits. The Hemophilia Growth and Development Study enrolled HIV-infected and HIV-uninfected patients and a group of nonhemophiliac siblings. After controlling for multiple factors, HCV mono-infection was not associated with deficits in adaptive behavior, intelligence, or attention/concentration.

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Chronic hepatitis C virus (HCV) infection may be associated with psychiatric, cognitive, and neuroimaging abnormalities.^{1–3} Implicating HCV as the cause of these abnormalities is complicated by the presence of frequent comorbidities, such as liver disease, substance abuse, and HIV coinfection.⁴ We have assessed the relationship between HCV infection and select measures of neurocognitive function in subjects enrolled in the Hemophilia Growth and Development Study (HGDS).

Methods. *Study population.* The HGDS enrolled 6 to 19 year olds from 14 United States Centers from 1989 through 1990. Of the hemophiliacs, HIV infection was present in 207, with 126 being HIV uninfected. Another 47 nonhemophiliac siblings were also enrolled.⁵ Informed consent was obtained from parents or legal guardians with consent or assent from all participants. HCV infection status was determined by antibody enzyme immunoassay followed by quantitative HCV RNA assay (bDNA, Versant, Bayer Healthcare Diagnostics). All but two individuals repeatedly negative by bDNA were confirmed negative by licensed qualitative HCV RNA testing. HCV infection (HCV RNA positive) was noted in 199 (96.1%) of the HIV-infected and 103 (81.7%) of the HIV-uninfected subjects with infection believed to have occurred shortly after birth when first exposed to factor VIII-containing products. All 47 siblings were HCV antibody negative. There were 70 individuals (23 hemophiliacs and 47 nonhemophiliacs) without active HIV or HCV infection.

Antiretroviral therapy was given at the discretion of the treating physician. At baseline, only 33.7% were taking antiretrovirals, the majority being a single nucleoside reverse transcriptase inhibitor. No subjects were treated for HCV infection before or at the time of enrollment into the HGDS.

Neuropsychological testing. Neuropsychological testing included the Vineland Adaptive Behavior Scales (Communication,

Daily Living, Socialization, and Composite standard scores), the age-appropriate Wechsler Intelligence scales, Wechsler Intelligence Scale for Children (WISC)–Revised or Wechsler Adult Intelligence Scale (WAIS)–Revised (Performance, Verbal and Full Scale IQ scores), and the Wechsler Digit Span, Vocabulary, and Block Design subtest scale scores as measures of attention/concentration, expressive vocabulary, and visual-spatial construction.

Statistical analysis. Baseline neurocognitive function was compared between each of three groups: those without HIV or HCV infection ($n = 70$), HIV-uninfected hemophiliacs with detectable serum HCV RNA ($n = 103$) and those with both HIV and HCV infection ($n = 199$). Analysis of covariance (ANCOVA) was performed adjusting for age, years of parent education, history of head trauma, academic problems (defined as repeating a grade or attendance in special remedial classes), and coordination and gait abnormalities. Significance was set at the 5% level after applying the Tukey multiple comparison procedure to the pairwise comparisons between the three groups. Assuming an R^2 of 0.10 between the outcome and the covariates in the ANCOVA model, we have 80% power to detect with 95% confidence a difference of 6.2 points between the uninfected and mono-infected groups, 5.6 points between the uninfected and coinfected groups, and 4.8 points between the mono-infected and coinfected groups for the Vineland scores and WISC/WAIS ($\sigma = 15$). For the Wechsler subtest scores ($\sigma = 3$), there is 80% power to detect a difference of 1.2 points between the uninfected and mono-infected groups, 1.1 points between the uninfected and coinfected groups, and 0.9 points between the mono-infected and coinfected groups.

Results. The ethnicities of the populations were similar: 71% to 74% white, 16% to 17% Hispanic, and 10% to 12% African-American. The HIV-infected group had a mean CD4⁺ T-lymphocyte count of 419 cells/ μ L and plasma HIV RNA level of 3.46 log₁₀ copies/mL. Other baseline characteristics are summarized in table 1. Baseline testing results are summarized in table 2. The HIV/HCV-uninfected group scored significantly higher than the dually infected group for the Vineland Daily Living standard score; however, there was no difference seen between the HCV mono-infected and uninfected subjects. All IQ scores were significantly higher for the HCV mono-infected than the uninfected group. Finally, for the Wechsler Vocabulary, the uninfected group scored lower than both the HCV mono-infected and HIV/HCV dually infected subjects. All tests were prospectively rated by the study neuropsychologist for validity. The lower number of subjects with valid Vineland scores was related to the fact that this is a parent- vs psychologist-administered test and is thus more frequently found to be invalid.

Discussion. In this study, we evaluated the relationship between HCV mono-infection and HIV/HCV dual infection and neurocognitive function. We compared these groups with each other and the unin-

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Table 1 Baseline characteristics of the cohorts

	HCV/HIV uninfected			HCV infected			HCV/HIV infected		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Baseline age, y*	70	12.4	3.8	103	11.4	3.1	199	13.2	3.1
Parents' education, years	69	13.9	2.5	103	13.2	2.8	198	13.2	3.1
Years in school*	70	5.8	3.6	101	4.9	3.1	196	6.5	3.1
HCV RNA, log ₁₀ *	—	—	—	102	5.6	1.2	199	6.4	1.1
ALT, log ₁₀	—	—	—	103	1.6	0.3	199	1.6	0.3
	n	%	Freq	n	%	Freq	n	%	Freq
History of head trauma*	70	12.9	9	103	44.7	46	199	35.2	70
Coordination and gait abnormalities	70	14.3	10	103	24.3	25	198	21.2	42
History of academic problems	70	7.1	5	103	4.9	5	199	12.1	24
17+ years old (tested on WAIS)	70	17.1	12	103	6.8	7	199	13.1	26

p values for Kruskal–Wallis tests (continuous covariates) and chi-square tests (dichotomous covariates) comparing differences between the three groups.

* *p* < 0.05.

HCV = hepatitis C virus; ALT = alanine aminotransferase; WAIS = Wechsler Adult Intelligence Scale.

ected controls for aspects of adaptive behavior, general intelligence, attention/concentration, expressive vocabulary, and visual–spatial construction. After adjusting for multiple factors, none of the 10 tests evaluated demonstrated significantly higher measures of function in those HCV uninfected compared with the HCV monoinfected group. Unexpectedly, the HCV-infected subjects had several significantly higher cognitive scores than those uninfected. This may reflect factors not controlled for, such as the fact that many of the uninfected were not hemophiliacs.

Several studies have shown that HCV infection is associated with increased depression, fatigue, and impaired quality of life (reviewed in⁶). More recent studies have suggested that neurocognitive abnormalities may be seen in this population, with particular deficits in attention, concentration, and information processing.^{1,7,8} One recent study showed that compared with uninfected controls, HCV-infected individuals had impaired attention and executive functioning, increased anxiety and depression, and abnormalities in the cerebral cortex

Table 2 Relationship between HIV and HCV infection status and results of neurocognitive testing

Neurocognitive test	HIV/HCV uninfected		HCV infected		HIV/HCV infected	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Vineland Communication	68	97.0 (1.8)	96	98.6 (1.6)	176	93.5 (1.2)
Vineland Daily Living	68	98.5 (1.5)	96	95.8 (1.3)	176	92.2 (1.1)*
Vineland Socialization	68	99.3 (1.7)	96	95.8 (1.4)	176	95.0 (1.1)
Vineland Composite	68	97.5 (1.7)	96	95.6 (1.4)	176	91.6 (1.1)
Performance IQ	69	104.2 (1.8)	99	107.2 (1.6)*	193	105.8 (1.1)
Verbal IQ	69	102.9 (1.7)	99	106.9 (1.6)*	193	102.9 (1.1)
Full Scale IQ	69	103.9 (1.7)	99	107.8 (1.6)*	193	104.7 (1.0)
Wechsler Digit Span	66	9.5 (0.3)	101	9.3 (0.3)	195	9.4 (0.2)
Wechsler Vocabulary	67	9.7 (0.4)	102	10.8 (0.3)*	195	10.3 (0.2)*
Wechsler Block Design	70	11.2 (0.4)	102	11.3 (0.3)	198	11.0 (0.2)

Pairwise comparisons by analysis of covariance were performed between each of the three groups adjusting for age, years of parents' education, history of head trauma, academic problems, coordination, and gait, as well as for multiple comparisons using the Tukey method. The Vineland scores are standard scores (mean = 100, SD = 15), and Wechsler subtest scores are scale scores (mean = 10, SD = 3).

* *p* < 0.05 for comparison with uninfected group.

HCV = hepatitis C virus.

measured by magnetic resonance spectroscopy.³ Another study demonstrated select deficits in executive functioning among those with advanced HIV infection who were coinfecting with HCV compared with those without HCV infection.⁹ A third study compared 27 HCV RNA–positive subjects with mild hepatic inflammation to 16 who were HCV antibody positive but RNA negative. In this study, they found cognitive impairment in the chronically infected group even after accounting for depression, fatigue, and history of IV drug use.⁸ Similar defects were observed in yet another small study,³ whereas another did not demonstrate psychometric test abnormalities among HCV-infected individuals.¹⁰

Although unlike other studies we did not see a relationship between HIV infection and outcomes, study populations are variable including differences in age, duration of infection, and the specific neurocognitive outcomes assessed. For example, the current study included children and adolescents enrolled from 1989 through 1990. Although this might bias the HIV-infected group, excluding rapid progressors, it would not have influenced enrollment and the comparisons made between those HCV monoinfected or uninfected. Moreover, most studies include seroprevalent cohorts with no information regarding duration of HIV or HCV infection or how outcomes might be influenced by selection bias.

Previous studies are limited by the analyses of data from small groups of randomly selected subjects from clinic populations or those enrolled in highly select cohort studies. Studies of such heterogeneous subjects are difficult to control for multiple confounders. In fact, one study showed that the frequencies of neuropsychological abnormalities were similar in those with chronic HCV infection without cirrhosis and those with other causes of liver disease.⁷ In addition to difficulty in controlling for severity of liver disease, most studies are limited in their ability to adjust for differences in duration of HCV infection and many potentially relevant socioeconomic factors. In contrast, our study included larger numbers of subjects than any previous report, and individuals in a natural history cohort representative of hemophiliacs in the community at that time.⁵ Furthermore, the groups had only modest differences in age, socioeconomic status (as defined by parent level of education), and duration of HCV infection (which approximates age); were not likely to be influenced by active or previous substance use, having an average age of 12 years; and were all known to have acquired HCV by exposure to blood products. Although baseline differences did exist (table 1), these variables were included in the models, and if relevant, the differences likely would have favored the uninfected group because they were older, had more years of schooling, and had less head trauma. Moreover, taking these factors out of the models did not change the major conclusions of the study. There were also trends toward differences in the number with history of academic problems and the

proportion tested on the WAIS test; however, when included in the ANCOVA models, these variables did not alter the main conclusions of the study. Finally, there was no evidence that differences in HCV RNA levels influenced outcomes when included in the ANCOVA model. Nevertheless, our study is limited by the cross-sectional design and the fact that HCV-infected subjects were all children or adolescents with hemophilia with an average duration of HCV infection of approximately 12 years. Moreover, there was no way to control for degree of hepatic inflammation in these individuals, and our analysis was limited to specific tests that assessed only select measures of neurocognitive function.

The high prevalence of HCV infection has led to increasing interest in the many extrahepatic manifestations of this disease. There have been conflicting reports regarding the association between HCV infection and neuropsychiatric and cognitive abnormalities in select groups of HCV- and HIV/HCV-infected individuals. Our study controlled for many comorbidities and psychosocial confounders and showed no relationship between HCV mono-infection and specific measures of neurobehavioral and cognitive function. Further research is needed to fully define what if any role HCV infection may play in the CNS.

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Appendix

The following individuals are the Center Directors, Study Coordinators, or Committee Chairs of the study: Children's Hospital Los Angeles: E. Gomperts, MD, W.Y. Wong, MD, F. Kaufman, MD, M. Nelson, MD, S. Pearson, RN; The New York Hospital–Cornell Medical Center: M. Hilgartner, MD, S. Cunningham-Rundles, PhD, I. Goldberg, RN; University of Texas Medical School, Houston: W.K. Hoots, MD, K. Loveland, PhD, M. Cantini, RN; The NIH, National Institute of Child Health and Human Development: A. Willoughby, MD, MPH, Robert Nugent, PhD; Rho, Inc.: S. Donfield, PhD; Baylor College of Medicine: C. Contant, Jr., PhD; University of Iowa Hospitals and Clinics: C.T. Kisker, MD, J. Stehbins, PhD, S. O'Conner, J. McKilip, RN; Tulane University: P. Sirois, PhD; Children's Hospital of Oklahoma: C. Sexauer, MD, H. Huszti, PhD, F. Kiplinger; S. Hawk, PA-C; Mount Sinai Medical Center: S. Arkin, MD, A. Forster, RN; University of Nebraska Medical Center: S. Swindells, MD, S. Richard; University of Texas Health Science Center, San Antonio: J. Mangos, MD, R. Davis, RN; Children's Hospital of Michigan: J. Lusher, MD, I. Warriar, MD, K. Baird-Cox, RN, MSN; Milton S. Hershey Medical Center: M.E. Eyster, MD, D. Ungar, MD, S. Neagley, RN, MA; Indiana Hemophilia and Thrombosis Center: A. Shapiro, MD, J. Morris, PNP; University of California–San Diego Medical Center: G. Davignon, MD, P. Mollen, RN; Kansas City School of Medicine, Children's Mercy Hospital: B. Wicklund, MD, A. Mehrhof, RN, MSN.

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NeuroImages

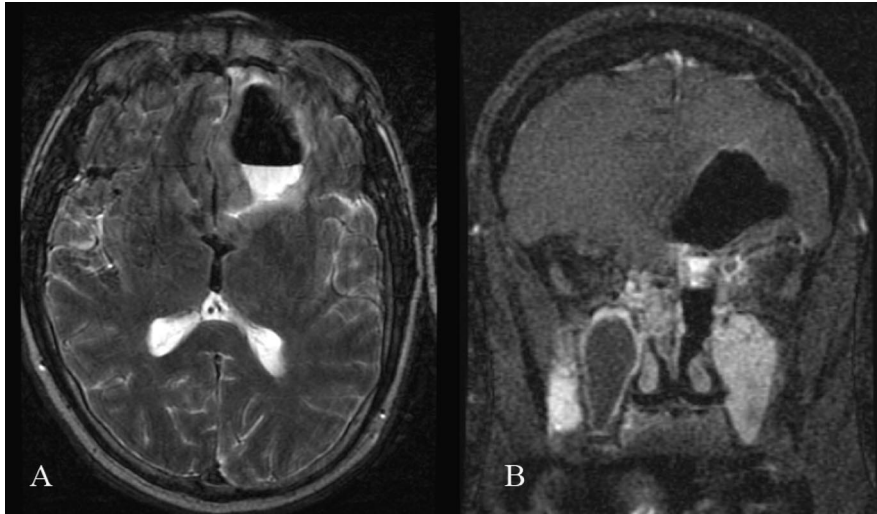


Figure. T2-weighted MRI without contrast demonstrates air-fluid levels in third ventricle and in left frontal lesion with mass effect evidenced by surrounding edema and subfalcine herniation (A). Coronal nonenhanced T1-weighted MRI demonstrates location of high-signal mass representing the fat pad between nasal cavity and left frontal air pocket (B).

Focal intraparenchymal tension pneumocephalus

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Pneumocephalus is a rare complication of craniofacial surgeries.^{1,2} A 48-year-old man presented with severe left frontal head-

aches, confusion, and right-sided myoclonic seizures 8 days after mucoperichondrial repair of CSF leak following left nasal polypectomy. Imaging studies demonstrated extensive pneumocephalus with an intraparenchymal air pocket causing subfalcine herniation adjacent to inserted fat pad, suggesting a ball-valve effect by the fat pad is likely the cause of focal air retention (figure). The patient made an excellent recovery following emergent bifrontal craniotomy, where air gushed out with needle insertion into the left frontal lobe.

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