Neuropsychological Aspects of Coinfection with HIV and Hepatitis C Virus

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Abstract

Infection with hepatitis C virus (HCV) is commonly seen in persons with human immunodeficiency virus (HIV) infection, because the viruses share risk factors for transmission; coinfection is a leading cause of morbidity and mortality among HIV-infected persons. Neuropsychological consequences of HIV infection are well established, and studies of HCV-infected persons have revealed neuropsychiatric dysfunction in this population as well. Investigators now are focusing on neuropsychological sequelae of coinfection with HIV and HCV, and preliminary results suggest that coinfection has a possible deleterious effect on global cognitive functioning consistent with frontal-subcortical dysfunction. Data on neuropsychiatric symptoms in coinfected persons are inconclusive at this time and are complicated by important differences in study populations (e.g., injection drug use and disease severity). This review summarizes what is known about neuropsychological aspects of monoinfection with HIV and HCV, as well as coinfection, discusses implications of these findings, and suggests future directions for this research area.

Coinfection with HIV and hepatitis C virus (HCV) is an understudied yet burgeoning health care crisis. Infection with HCV is the most common chronic blood-borne infection in the United States [1]. An estimated 2.7 million Americans are chronically infected with HCV, and, because many of these persons are <50 years old, a significant future disease burden is imminent. Many of these persons will develop cirrhosis and associated complications, resulting in disability and, for some, premature death. High rates of morbidity and mortality also affect the nearly 1 million Americans and 38 million persons worldwide who are infected with HIV. Epidemiological data on the rate of coinfection are limited, although recent large-scale studies suggest that about one-third of all persons infected with HIV are coinfected with HCV, with rates dramatically higher (i.e., 60%–90%) among injection drug users (IDUs) [2].

HIV and HCV share common routes of transmission and common risk factors and may also share common neurocognitive and neuropsychiatric consequences. Rates of neuropsychiatric dysfunction, particularly depression, anxiety, apathy, and fatigue, are elevated among persons infected with HIV [3], persons infected with HCV [4], and coinfected persons [3]. Although it is well established that HIV infection can lead to significant neurocognitive impairment, the deleterious effect of HCV on cognition has only recently been appreciated. Even less is known about the neurocognitive consequences of coinfection, although several recent studies of HCV-

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infected subjects have revealed a constellation of deficits similar to that seen in HIV monoinfection [5,6]. Neurometabolic commonalities, such as increased ratios of choline to creatine (Cho:Cr) in frontostriatal regions, also have been found by use of proton magnetic resonance spectroscopy in both HIV and HCV monoinfection [7-9]. Given the neurophysiological and neurobehavioral commonalties between these 2 disease processes, it is not unreasonable to hypothesize that coinfection may be associated with increased severity of neuropsychological impairment and accelerated decrease in function over time. Here, we review what is known about the cognitive and psychiatric effects of HIV and HCV infection and coinfection with HIV and HCV, with a focus on data from our research groups. We also discuss issues that complicate research of the neuropsychology of coinfection with HIV and HCV and identify directions for future study.

NEUROCOGNITIVE FEATURES OF HIV INFECTION

The adverse effects of HIV infection on cognitive function are well established (reviewed in [10]). Manifestations of neurocognitive dysfunction range from subtle and mild cognitive changes to frank dementia syndromes. Typically, the degree and incidence of neurocognitive impairment increase with disease progression and/or severity of immunocompromise. The American Academy of Neurology divides neurobehavioral disorders into 2 subgroups: HIV-associated dementia and HIV-associated minor cognitive-motor disorder. The major distinction between the categories is related to the severity of impairment. Memory impairment (characterized especially by retrieval deficits), motor and psychomotor slowing, attentional disruption, and executive systems dysfunction have all been repeatedly observed among HIV-positive persons. Slowed information processing is a central feature of the neurocognitive compromise seen in persons with HIV infection and may, in fact, underlie deficits seen in other cognitive domains [11]. A number of studies, including several from our group [12,13], have successfully used measures borrowed from the cognitive and experimental psychology literature to better isolate components of attention and processing speed that may be particularly vulnerable to the effects of HIV infection. Studies making use of cognitive-experimental tasks generally converge to suggest that HIV-infected persons show compromise on tasks that place high demands on controlled (versus automatic) attentional processing resources [14].

NEUROPSYCHIATRIC FEATURES OF HIV INFECTION

Several studies have shown that psychiatric disorders, including mood, anxiety, and substance use disorders, are more prevalent among HIV-positive adults than among the general population [15]. Neuropsychiatric symptoms such as apathy and irritability are also common in HIV-infected adults [16], as are elevated rates of depressive symptoms [15]. Although rates of psychiatric disorders do not tend to differ markedly by disease stage, neuropsychiatric features such as apathy and irritability, which may be more likely to reflect HIV-associated CNS involvement than are depression or anxiety, are more common with advanced disease [17]. Higher prevalences of psychiatric disorders and neuropsychiatric symptoms have been attributed to both direct (i.e., disease-related) and secondary etiologies. For example, depression, apathy, and irritability may, in part, be a primary consequence of the neurological effects of the virus. Disease-related subcortical pathologic abnormalities may lead to neuropsychiatric disturbance among a subset of HIV-positive persons, and work from our laboratory has linked apathy, irritability, and aspects of depression to neurocognitive dysfunction in HIV and posited a common etiology for both [16,17]. In addition, depression and anxiety may be a reaction to the losses, medical stressors, compromised social support, marginalization, and stigmatization associated with HIV/AIDS. The pattern of neurocognitive and neuropsychiatric symptoms is suggestive of disruption to the circuits that connect the prefrontal cortex with subcortical structures and is consistent with findings from studies using

structural neuroimaging [18], functional neuroimaging [19], and autopsy [20], all of which suggest prominent subcortical brain involvement.

NEUROCOGNITIVE FEATURES OF HCV INFECTION

Until recently, neurocognitive dysfunction in patients with chronic liver disease was thought to be associated with decompensated cirrhosis (i.e., hepatic encephalopathy). However, with the epidemic of HCV infection came increasing complaints of neurocognitive difficulties, especially problems with concentration and slowed information processing speed, by persons without cirrhosis. The prevalence of neurocognitive dysfunction in persons infected with HCV was explored by Hilsabeck et al. [5,6], who found that about one-third of HCV-infected patients seen in a tertiary care liver clinic performed in the impaired range on ≥2 neuropsychological measures. Percentages of impaired performances by measure are presented in table 1. This rate of neurocognitive impairment is similar to rates reported among HIV-infected patients and ~2–3 times greater than those reported among healthy subjects [21].

Similar to the case with HIV infection, the pattern of neurocognitive deficits in HCV-infected persons is suggestive of frontal-subcortical dysfunction, with complex attention/concentration and information processing and psychomotor speed preferentially impaired [5,6,9]. Findings by use of proton magnetic resonance spectroscopy also indicate frontal-subcortical changes in persons with HCV [8,9,22]. Forton et al. [8,9] found that HCV-infected persons had significantly higher Cho:Cr values in the basal ganglia and frontal white matter than did persons infected with hepatitis B virus and healthy volunteers. They also showed that HCV-infected persons were impaired on more neuropsychological tests than persons who had cleared HCV infection and healthy volunteers, and persons with HCV infection who were cognitively impaired had significantly higher Cho:Cr values in the basal ganglia than did unimpaired HCV-infected persons and healthy volunteers [9]. In a sample of methamphetamine-dependent persons, Taylor et al. [22] found that persons infected with HCV tended to have lower levels of N-acetylaspartate in the frontal white matter than did persons without HCV infection, and a larger percentage of HCV-infected persons than those without HCV infection were rated as impaired on neuropsychological tests (83% vs. 50%).

The etiology of neurocognitive dysfunction in patients infected with HCV is not yet known. Increasing evidence suggests that there may be a direct effect of the virus on the brain via a "Trojan horse" mechanism similar to that hypothesized to occur in HIV infection [23]. This possibility is supported by data showing selective distribution of HCV quasi species in cells of monocytic lineage [23,24]. Indirect effects of HCV on brain functioning also are possible via changes in neuroendocrine systems, neurotransmitter function, and/or secondary cytokines. Neurocognitive dysfunction in HCV-infected persons has not been found to relate significantly to history of injection drug use, liver function tests, virus load, HCV genotype, or self-reported cognitive difficulties, affective state, fatigue, or quality of life [6,23,25]. Increasing levels of fibrosis, poor physical and general health, and comorbid medical conditions (e.g., HIV or hepatitis B virus infection) have been shown to be associated with greater neurocognitive impairment, however [5,6,25].

NEUROPSYCHIATRIC FEATURES OF HCV INFECTION

Neuropsychiatric symptomatology is experienced by most persons infected with HCV during the course of their disease and may increase as time passes without hope of a cure [26]. Fontana et al. [27] reported clinically significant emotional distress in 35% of patients infected with HCV, with a strong relationship noted between high levels of neuropsychiatric symptomatology and decreased health-related quality of life. A compounding factor is that treatment for HCV infection, usually IFN combined with ribavirin, also is associated with

increased psychiatric symptomatology, including depression, anxiety, fatigue, mania, and, in rare cases, suicide [28].

Comorbid psychiatric disorders are the rule, rather than the exception, in persons with HCV infection. Lifetime rates of psychiatric disorders range from 82% to 95%, with substance use disorders being most common [29,30]. Current rates of psychiatric disorders also are high, ranging from 31% to 58% [29,30]. The most common psychiatric disorder in persons infected with HCV is depression, with ~28% of patients meeting diagnostic criteria for major depressive disorder, dysthymia, or depressive disorders not otherwise specified from the Diagnostic and Statistical Manual of Mental Disorders, 4th revision. Anxiety disorders are the second most common, with rates ranging from 18% to 26%, and generalized anxiety disorder and posttraumatic stress disorder are the most prevalent, depending on the setting (i.e., tertiary care liver clinic vs. Department of Veterans Affairs clinic). Bipolar disorder, psychotic disorders, and personality disorders have been examined less often, but a preliminary study of a population of veterans found prevalences of 6%, 17%, and 30%, respectively [30]. The most common neuropsychiatric symptom reported by HCV-infected persons is fatigue, with prevalence ranging from 39% to 100% [31].

The high prevalence of psychiatric disorders in patients with HCV infection likely is multifactorial. First, there is the possibility that having a psychiatric disorder places one at risk for contracting HCV, given that persons with psychiatric disorders may be more likely to engage in high-risk behaviors [32,33]. Second, persons with histories of psychiatric disorders are at risk for relapse, especially when presented with a major life stressor, such as the diagnosis of a chronic medical illness. Third, pathophysiological explanations similar to those suggested above for neurocognitive dysfunction have been postulated, which may be compounded by increased production of proinflammatory cytokines related to psychological stress associated with having a chronic medical illness [34]. Finally, preliminary findings suggest that genetic factors may play a role in susceptibility to neuropsychiatric symptoms; a recent study reported that HCV-infected persons with histories of psychiatric disorders were more likely to have at least one apolipoprotein E ε4 allele than were those without histories of psychiatric disorders [35].

NEUROCOGNITIVE FEATURES OF COINFECTION WITH HIV AND HCV

Results of studies examining the effects of coinfection with HIV and HCV on neurocognitive functioning have been mixed. Letendre et al. [36] were among the first to examine this issue, reporting that persons who were coinfected were more likely to exhibit overall neurocognitive impairment than were persons infected with either HIV or HCV alone, suggesting that there was a possible synergistic effect of these infections on the CNS. A similar conclusion was suggested by data showing that coinfected persons demonstrated significantly slower reaction times than did persons infected with either virus alone [37,38] and that significantly more persons with advanced HIV and HCV coinfection than those with advanced HIV monoinfection met criteria for AIDS dementia complex [39].

In contrast, other data have failed to show significant differences between coinfected and monoinfected persons in other neurocognitive domains, although trends for greater impairment in coinfected persons were evident [38-40]. One study found no differences between persons infected with HIV only, HCV only, or both viruses by use of measures of intelligence, attention, and memory and electrophysiological motor tests [38]. In a sample of patients with advanced HIV infection, there were no differences between those with and without HCV infection by use of measures of psychomotor speed, working memory, learning, memory, or executive functioning [39]. The only exception was with a measure of nonverbal problem solving, in which the coinfected group made significantly more perseverative responses than did persons

with HIV infection alone. Perry et al. [40] found no significant differences between HCV-infected and coinfected persons by use of measures targeting complex attention and psychomotor speed.

To further examine the effect of coinfection with HIV and HCV on neuropsychological function, we performed secondary analyses on a cohort of 195 HIV-infected adults recruited as part of a study examining predictors of medication adherence [41]. Although HCV status was not a direct focus of that study, ~13% of those subjects ($n = 25$) were coinfected with HIV and HCV. We compared the performance of coinfected subjects with that of HIV-monoinfected subjects on a comprehensive battery of neuropsychological tests and found that 80% of the coinfected group was classified as neurocognitively impaired, versus 69% of the HIV-monoinfected group (table 2). Examination of the component cognitive domains revealed that this difference was largely attributable to an increased rate of psychomotor slowing among the coinfected group: 84% demonstrated significant psychomotor slowing, versus 56% of the HIV-monoinfected group ($\chi^2 = 7.3$; $P = .007$). The groups did not differ according to measures of other cognitive functions.

Several hypotheses have been advanced to explain greater neurocognitive impairment in coinfected patients. A synergistic effect of the 2 viruses on neurocognitive functioning has been suggested, given that HCV replication has been documented in the same cells as HIV (i.e., monocytes/macrophages and T and B lymphocytes), and there is preliminary evidence that HIV infection facilitates HCV replication in monocytes/macrophages [42]. Similarly, coinfection could have an additive effect on activation of the immune system. It also is possible that increased neurocognitive deficits in coinfected persons are related to decompensated liver functioning, because HIV has been shown to accelerate progression of fibrosis in persons infected with HCV [43]. Additional studies of persons with broader spectra of both diseases are needed to understand the relationship of neurocognitive functioning and disease severity in coinfected persons.

NEUROPSYCHIATRIC FEATURES OF COINFECTION WITH HIV AND HCV

Even less is known about neuropsychiatric symptoms of coinfected patients. In one of the few studies investigating this issue, Grassi et al. [44] studied 3 groups of IDUs, those with HCV infection, those with HIV infection, and those with neither infection. Of IDUs with HIV infection, 83% were coinfected with HCV. Therefore, the HIV group in this study is conceptualized more accurately as a coinfected group. Results revealed that the HCV-monoinfected group reported significantly greater symptomatology than did the coinfected group on scales measuring obsessive-compulsive features, interpersonal sensitivity, phobic anxiety, paranoid ideation, and psychoticism. The only measure for which the coinfected group reported significantly greater symptomatology was somatization. Interestingly, the group of IDUs without infection often reported psychiatric symptomatology greater than that of the coinfected group but lower than that of the HCV-monoinfected group, suggesting that psychological distress manifested in this cohort of IDUs is related to variables other than infection. Our group partially replicated these findings, showing that coinfected persons reported a significantly greater number of physical symptoms than did persons with HIV or HCV infection alone, but there were no significant group differences with regard to depression, anxiety, fatigue, or quality of life [45]. Coinfected persons also reported significantly greater hostility and cognitive inefficiency than did either monoinfected group.

With regard to psychiatric disorders, one study showed that coinfected persons were significantly more likely than HIV-infected persons to have a history of dependence on cocaine, opiates, and stimulants, as well as a history of substance-induced depression [39]. Rates of current dependence did not differ significantly between the 2 groups, with rates ranging from

a high of 16%–24% for current dependence on cocaine to a low of 3%–7% for dependence on cannabis. However, rates of current abuse were highest for cannabis (~25%) but were low for other substances (0%–7%) and did not differ significantly between the 2 groups. There also were no significant group differences in past or current rates of other primary psychiatric disorders, including mood disorders, anxiety disorders, or childhood conduct and antisocial personality disorders. Depression was the most common disorder by far, reaching rates of 71% and 62% for past depression in coinfected and HIV-infected persons, respectively, and 42% for current rates in both groups. Past dysthymia, past posttraumatic stress disorder, and childhood conduct disorder were the next most prevalent, with rates for each ranging between 16% and 19% in both groups.

Our group examined rates of lifetime psychiatric disorder and drug or alcohol abuse again with the above-described cohort of 195 HIV-infected persons, 25 of whom were coinfected [41]. As can be seen in table 2, the coinfected cohort evidenced a higher rate of both current and lifetime alcohol abuse and drug abuse. Contrary to the findings of Ryan et al. [39], the coinfected cohort in our study [41] did not demonstrate significantly higher rates of lifetime psychiatric illness.

CONCLUSIONS AND FUTURE DIRECTIONS

Although only a few studies have been conducted, preliminary data suggest that overall neurocognitive functioning is more impaired in coinfected persons than in persons infected with either HIV or HCV alone. The reasons for this are unclear but may be related to additive effects of both infections on specific brain sites, especially frontal-subcortical regions. Slowed reaction time and perseverative responding were more common in coinfected persons, warranting further study. Future examination of neurocognitive functioning by use of proton magnetic resonance spectroscopy and functional MRI, in conjunction with neuropsychological measures, will shed light on brain regions most affected and their functional repercussions. Studies focusing on relationships between brain functioning, viral replication within cells of monocytic lineage, and cytokine levels will help discern the relative contributions of the viruses themselves and the inflammatory process associated with chronic infection.

Data on neuropsychiatric functioning among coinfected persons are even more limited, and important differences in study samples may influence results significantly. Coinfected persons appear to have a greater number of somatic concerns than do persons with HIV or HCV infection alone and are more likely to have a history of substance dependence than are HIV-monoinfected persons. However, coinfected persons do not report more neuropsychiatric symptoms or a higher prevalence of other psychiatric disorders than do monoinfected persons. In fact, one study showed that IDUs without HIV or HCV infection indicated greater psychological distress than did coinfected persons. Comparisons between cohorts of persons who acquired coinfection via injection drug use versus other modes of transmission are needed to clarify the role of premorbid characteristics. In addition, prospective longitudinal studies that include persons with a wide range of disease severity and that investigate relationships among levels of cytokines and neurotransmitter metabolites, especially serotonin, could shed light on pathophysiological mechanisms.

An area that has yet to be examined closely in coinfected patients is adverse effects of antiviral therapy for HCV infection. As noted above, neuropsychiatric symptoms are commonly associated with antiviral therapy in HCV-infected persons, and preliminary data suggest that antiviral therapy also affects neurocognitive functioning [46]. It is possible that coinfected patients may be more adversely affected by antiviral therapy for HCV infection, given evidence that persons with pretreatment psychiatric symptoms and CNS disorders may be at greater risk for developing neuropsychiatric adverse effects [27]. In addition, exploration of genetic

markers, such as apolipoprotein E ε4 allele, could shed additional light on which coinfected persons are more susceptible to neuropsychiatric adverse effects of IFN, as well as neuropsychological dysfunction in general.

Although this area of research is clearly an important area of inquiry, the determination of causes of cognitive and psychiatric dysfunction among coinfected persons is complicated by the often heavy and chronic use of neurotoxic drugs among this population. It is generally well established that chronic and/ or heavy use of many of the illicit substances that are common in the histories of coinfected persons (e.g., opiates, stimulants, and synthetic drugs) can cause cognitive and psychiatric disturbance [47]. As noted above, those persons who acquired their coinfection via injection drug use are likely to have longstanding histories of substance dependence. Obviously, without the inclusion of relevant control subjects (i.e., noninfected IDUs) in study designs, it will be difficult to go beyond the descriptive and arrive at mechanisms or causes of cognitive dysfunction and/or psychiatric disturbance.

In conclusion, much can be learned from the unfortunate epidemic of HCV infection that is now a leading cause of morbidity and mortality in persons with HIV infection [48]. Study of similarities and differences in neuropsychological dysfunction between coinfected and monoinfected persons can afford new insights into CNS–immune system interactions, as well as influences of genetics and environment on etiology and progression. With greater understanding of the etiology and course of neuropsychological consequences of chronic infection, new avenues for prevention and treatment can be developed, which may benefit not only persons with HIV and/or HCV infection but perhaps persons with neuropsychological dysfunction associated with other diseases involving immunologic components.

Acknowledgments

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Table 1

Percentage of impaired performances, by measure, in patients with hepatitis C virus infection

Measure	Impaired performances, %
BVMT-R copy	9.5
BVMT-R learning	14.3
BVMT-R % recalled	15.7
BVMT-R recognition	9.5
Symbol search	23.8
TMT part A	23.8
TMT part B	19.0
SDMT	38.1

NOTE. BVMT-R, Brief Visuospatial Memory Test-Revised; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test. Reprinted from Hilsabeck et al. [6], with permission from the Cambridge University Press.

Table 2

Percentage of subjects infected with HIV or with HIV and hepatitis C virus (HCV) who had cognitive or psychiatric disorders

Domain/disorder	Coinfected with HIV and HCV	HIV-infected; HCV-negative	*P*
Speed of information processing	84	56	.007
Learning and memory	64	58	.56
Attention	52	58	.61
Executive functioning	52	57	.61
Verbal fluency	25	29	.70
Motor speed	68	67	.95
Global cognitive functioning	80	69	.25
Past major depressive episode	60	47	.24
Past bipolar disorder	16	12	.52
Past psychotic disorder	4	6	.72
Alcohol abuse or dependence			
Current	20	8	.04
Past	76	45	.003
Drug abuse or dependence			
Current	28	8	.001
Past	84	58	.01

NOTE. Data are from Hinkin et al. [41].