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Hepatitis C and Cognitive Impairment

Robin C. Hilsabeck, PhD

Texas Tech University Health Sciences Center

Tarek I. Hassanein, MD

University of California, San Diego

Cognitive impairment, or difficulty in thinking abilities, has long been recognized as a consequence of chronic liver disease. However, until recently, cognitive impairment was considered a complication of cirrhosis associated with hepatic encephalopathy (HE). Patients with HE may demonstrate subtle reversible cognitive difficulties, such as poor attention and concentration, or they may suffer severe cognitive deficits, such as disorientation and fluctuating consciousness that can result in coma and death [1]. HE originally was thought to be a metabolic disorder caused by the injured liver's inability to remove toxins effectively from the blood stream, which then were carried to the brain, altering its function. Current theories postulate that HE might also result from a variety of brain abnormalities, including vascular changes, brain cell (e.g., astrocyte) swelling, hemorrhage, and the deposition of certain metals in the brain stem [2-3]. New assessment techniques also have identified particular brain structures and functions that appear to be differentially affected by HE, resulting from both acute and chronic liver disease [4-5].

With the epidemic of hepatitis C virus (HCV) infection came increasing numbers of patients without cirrhosis complaining of subtle cognitive impairment, most commonly difficulty in concentration and slowed thinking. These complaints led to investigations of possible cognitive impairment in patients with HCV presenting with mild (noncirrhotic) liver disease. Using a neuroimaging technique called proton magnetic-resonance spectroscopy (MRS), Forton and colleagues were among the first to report cerebral metabolite abnormalities suggestive of frontal-subcortical dysfunction in patients with mild chronic HCV infection [6-7]. Specifically, they reported abnormalities in the white matter and basal ganglia of patients with chronic HCV that were not evident in patients with chronic hepatitis B or healthy volunteers [6]. These researchers later found that HCV-infected patients were impaired on more cognitive tasks than patients who had cleared HCV and healthy volunteers, with the most significant differences occurring on measures of concentration and information processing speed [7]. Moreover, HCV-infected patients who were impaired on two or more cognitive tasks exhibited greater cerebral metabolite abnormalities in the white matter and basal ganglia than unimpaired HCV patients and healthy volunteers. Depression, fatigue, and history of intravenous drug use (IVDU) could not account for the group differences in cognitive functioning. However, patients who had cleared the HCV infection with treatment did not show these neuroimaging abnormalities.

The prevalence of cognitive dysfunction in patients with chronic HCV was investigated by Hilsabeck and colleagues who found that the proportion of impaired performances ranged from 0% on a design copy task to 49% on a measure of sustained attention and concentration [8]. Cognitive performances of patients with HCV did not differ significantly from patients with other types of chronic liver diseases. However, patients with HCV plus a second chronic medical condition, such as alcoholic hepatitis or human immunodeficiency virus (HIV), demonstrated

greater levels of cognitive dysfunction. In addition, patients with more advanced liver disease and increasing levels of fibrosis were more likely to show greater cognitive impairment. The pattern of cognitive deficits was suggestive of frontal-subcortical dysfunction. These findings were replicated in a separate sample of HCV-infected patients using slightly different cognitive tests [9]. Prevalence of cognitive impairment was found to range from 9% on a figure copy task to 38% on a measure of complex attention, visual scanning and tracking, and psychomotor speed. As before, greater severity of liver disease and fibrosis was associated with poorer cognitive functioning. Performances on cognitive tests were not related to perceived cognitive dysfunction, depression, anxiety, or fatigue, replicating and extending the findings of Forton and colleagues [7].

An independent group of researchers recently replicated the prevalence rate of cognitive impairment in patients with hepatitis C, reporting that 39% of their sample were cognitively impaired on at least four of 12 cognitive tests [10]. They also found no association between cognitive impairment and history of IVDU, history of psychiatric disorder, and depressive symptoms. In contrast to findings of Hilsabeck and colleagues [8], these investigators reported no relationship between cognitive impairment and fibrosis stage, which may be due to their exclusion of patients with advanced liver disease (i.e., exclusion of patients with severe fibrosis and cirrhosis). Predictors of cognitive impairment in their sample were lower pre-illness intelligence and use of antidepressant medication. These findings suggest that HCV-infected patients with lower cognitive reserve may be more susceptible to cognitive impairment associated with HCV infection. The association between greater cognitive impairment and antidepressant medication usage is unclear, and the investigators did not report which antidepressants were used by their sample. Replication of these findings is needed to establish the validity of these relationships before firm conclusions can be drawn.

The etiology of cognitive dysfunction exhibited by patients with HCV is unknown. Increasing evidence suggests that there may be a direct effect of the virus on brain functioning via a "trojan horse" mechanism, similar to that hypothesized to occur in HIV-infected patients [7,11]. The "trojan horse" hypothesis suggests that cerebral dysfunction occurs secondary to infection of monocytes, which are believed to replace microglial cells. Microglial cells are located predominantly in the cerebral white matter and are known to release excitatory amino acids that can induce neuronal cell death. Moreover, microglia can produce neurotoxins and other neurochemicals that can influence cognitive functioning [12]. The possibility of a "trojan horse" mechanism in HCV is suggested by data showing selective distribution of HCV quasi-species in cells of monocytic lineage [13-15].

Indirect effects of HCV on brain functioning also are possible via production of secondary cytokines (e.g., interferons, interleukins). Cytokines may cross the blood brain barrier and/or interact with the cerebral vascular endothelium and generate secondary messengers, which can affect cognitive functioning via multiple mechanisms that can influence arousal, initiation, working memory, psychomotor movements, and mood [15-19]. The possibility that cognitive dysfunction may be related to personality characteristics and/or psychiatric disturbances appears unlikely given the consistent reports of no association between these variables and cognitive impairment. More likely is the possibility that psychiatric symptoms, in part, are manifestations of the cerebral effect of HCV.

The cognitive dysfunction evidenced by patients with chronic HCV is important to note as it may affect quality of life. Poor attention and concentration and problems with working memory can interfere with one's ability to learn new information, focus on a single task for a prolonged length of time, and/or perform multiple tasks simultaneously without error. Slowed thinking and psychomotor speed, especially in combination with impaired attention and concentration, can result in prolonged periods of time needed to complete even routine tasks. Cognitive problems such as these may influence medical care, as cognitively impaired patients may fail to remember (or remember incorrectly) important details about their liver disease, treatment regimen, and/or physicians' recommendations. They may experience difficulties performing household and job duties as efficiently and accurately as before. Ultimately, many patients may experience frustration and mood problems, such as depression and anxiety, which can exacerbate cognitive deficits.

In summary, cognitive impairment has long been associated with chronic liver disease, although it was believed to occur only in cirrhotic patients with HE. Recent research has demonstrated that cognitive dysfunction is apparent in patients with HCV with and without

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cirrhosis. Approximately one-third of HCV-infected patients exhibit cognitive impairment, with the likelihood of impairment increasing with the presence of greater levels of fibrosis and/or a comorbid chronic medical condition. Attention and concentration, working memory, and psychomotor speed are the cognitive functions most likely to be impaired, suggesting a proclivity for frontal-subcortical systems, which is consistent with metabolite abnormalities found in studies using MRS techniques. The etiology of cognitive impairments associated with HCV is unclear at this time, but evidence for both direct and indirect mechanisms has been presented. Further research to confirm these observations in larger numbers of patients and in all possible etiologies of chronic liver disease is needed so that treatment options can be identified and tested. Future research also could address predictors of cognitive impairment in HCV patients, as well as the effect of antiviral therapy on cognitive functioning.

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