Neurologic Manifestations of Hepatitis C Virus Infection

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KEYWORDS

• Hepatitis C • Fatigue • Neurocognition • MR spectroscopy • Interferon • Ledipasvir/sofosbuvir • Cerebrovascular disease

KEY POINTS

- The extrahepatic manifestations of hepatitis C virus (HCV) in the brain include neurocognitive dysfunction, which is manifested by subtle changes in memory, attention, and processing speed.
- Neurocognitive defects are independent of the histologic stage of disease and may be induced by a direct effect of HCV on microglial cells or mediated by systemic cytokines crossing the blood-brain barrier.
- Magnetic resonance spectroscopy demonstrates abnormal metabolism in basal ganglia and prefrontal and frontal cortex, which has been associated with fatigue and abnormal neurocognitive testing.
- Interferon and direct-acting antiviral therapy can improve cerebral metabolism and neurocognition if a sustained virologic response is obtained.
- Cerebrovascular events and mortality are increased in patients with HCV and may be through an increased risk of carotid artery disease and plaque formation.

INTRODUCTION

The neurologic manifestations of hepatitis C virus (HCV) include cognitive impairment that can lead to brain fog and fatigue, markedly impair quality of life, and increase risk of cerebrovascular events and stroke. The mechanisms by which HCV results in these neurologic syndromes is not fully elucidated, but evidence exists that these represent true extrahepatic manifestations of chronic HCV infection.

Cognitive Impairment: Pathophysiology

Our understanding of the exact pathophysiology of neurocognitive defects in HCV is not fully elucidated. Initially, impairment in cognition was thought to be related

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predominantly to progressive liver disease with the development of cirrhosis and subclinical encephalopathy secondary to portal-systemic shunting and increased ammonia and astrocyte swelling. More recently, the recognition that memory impairment, fluctuating disorientation, and fatigue were independent of liver fibrosis led to the concept of a direct effect of HCV on cognition.[1,2]

There is evidence that HCV can cross the blood-brain barrier and even replicate in the brain. HCV has been suggested to enter the brain carried by infected monocytes as a Trojan horse and subsequently infect microglial cells, which are essentially macrophages derived from a monocyte lineage.[3–6] HCV negative strand virus, suggesting a replicative intermediate has been found in the brain, and HCV can also be detected in the cerebrospinal fluid (CSF). However, there is little correlation of CSF levels of HCV with serum HCV viral load; neurocognitive defects are not clearly associated with overall viral burden or viral replication.

An alternative theory of the effect of HCV on neurocognition suggests that it is a secondary effect of the chronic activation of the immune system and mediated by cytokines.[7–9] Chronic HCV infection is associated with elevated systemic cytokine levels including interferon (IFN)-α and tumor necrosis factor α; these have been shown to cross the blood-brain barrier and affect brain functioning[10–12] where they can cause release of secondary messengers from the vascular endothelium, including prostaglandins and nitric oxide. Cytokines in the CNS can also stimulate neuroendocrine pathways and neurotransmission.

Cognitive impairment: clinical manifestations

The hallmarks of cognitive dysfunction in HCV are a subtle difficulty in concentration and slowed thinking. This is often clinically manifested as difficulty with higher functioning particularly with numbers, sustained attention, psychomotor speed, and learning memory. The pattern of impairment suggests involvement of frontal-subcortical pathways. The constellation of symptoms has been described by patients with HCV as a brain fog, which is an excellent description of the impact on individuals. Hilsabeck and colleagues[13] demonstrated, using a battery of neuropsychological tests, the impaired performance particularly in sustained attention (82%) within a cohort of 66 patients with chronic HCV. Patients with chronic HCV performed less well than a control population with other liver diseases, and there was an association of worsening performance both with the presence of comorbidities and with increased fibrosis. Other studies have confirmed these findings and again documented impairment of working memory, sustained attention, and processing speed.[14,15] Interestingly, this pattern of neurocognitive abnormalities involving the subcortical neurocircuitry is similar to that reported for patients with human immunodeficiency virus infection.

Cognitive impairment and comorbidities

The differentiation of cognitive dysfunction secondary to HCV from comorbidities associated with HCV, such as drug and alcohol addiction or psychiatric disease, is complex. Intravenous drug use (IVDU) and alcohol addiction are extremely common comorbidities and seen in up to 70% and 30% of patients with HCV, respectively, and in themselves have well described associations with cognitive impairment.[16–20] Forton and colleagues studied a group of patients with HCV with active infection, a group with risk factors for HCV but RNA negative, and a matched population of patients with HCV who had been successfully treated and cleared the virus but with matching premorbid conditions. The HCV-infected group was impaired on more neuropsychological tests than the HCV-cleared group; these finding were independent of