# 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)-$\alpha$ and tumor necrosis factor $\alpha$; 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

a history of IVDU, which was reported in 50% of the patients. Kramer and colleagues[21] compared a group of patients with HCV with minimal alcohol consumption with a group with moderate to severe alcohol consumption and found no effect of alcohol history on the cognitive impairment associated with HCV.[21,22] These studies provide evidence of an association of cognitive impairment with HCV regardless of a history of premorbid substance abuse.

Psychiatric disease is also common in patients with HCV, with up to 40% of patients with HCV meeting diagnostic criteria for a concurrent active psychiatric disorder, including anxiety, depression, bipolar disorder, posttraumatic stress disorder, or personality disorders.[18–20] These patients frequently manifest fatigue, anxiety, and depression; all of these may impact neurocognition particularly on measures of concentration, attention, and processing speed.[15] In addition, many neuropsychiatric medications may also affect sensory awareness and neurocognition. Although there is little doubt that these psychiatric syndromes can all worsen neurocognition, the impairment of cognition in patients with HCV has been described independently of prior or active psychiatric conditions again suggesting the independent association of HCV and cognitive impairment.

### *Cognitive impairment: electroencephalogram and imaging studies*

Further evidence for impaired neurocognition comes from electroencephalogram (EEG) and imaging studies performed in patients with HCV. Weissenborn and colleagues[15] compared a group of patients with HCV with mild versus moderate fatigue to a matched controlled population using neuropsychiatric testing, EEG, and cerebral proton MRI with spectroscopy (MRS). The patients with HCV had evidence of cognitive impairment; 25% had slowing of their mean dominant frequency on EEG, and this was seen in patients with both mild and moderate fatigue. There was a correlation of the slowing on EEG to performance characteristics on the neuropsychological tests, particularly on verbal performance, Weschler intelligence test, and working memory tasks.

MRS has the ability to examine the ratio of neural metabolites in areas of the central nervous system (CNS) by targeting different regions of the brain. Commonly targeted areas include the basal ganglia, frontal cortex and prefrontal cortex all of which are involved in neurocognitive processes. The metabolites most frequently measured are N-acetyl aspartate (NAA), choline (Cho), and myoinositol (MI); these are expressed as a ratio when compared with the control metabolite creatine (Cr). Cho and MI are putative markers for glial cell inflammation and activation that could be a direct result of HCV replication in microglial cells or as a secondary effect of peripherally derived proinflammatory cytokines, as discussed previously. NAA is a marker of neuronal health and viability and is reduced in diseases whereby there is neuronal loss particularly in the gray matter.

MRS has shown that HCV-infected patients have elevated levels of Cho in certain brain regions (basal ganglia, white matter, occipital gray matter) and reduced levels of NAA compared with uninfected patients, irrespective of the degree of liver damage and unrelated to hepatic encephalopathy.[15,23] More recently HCV-infected patients were shown to have elevated MI/Cr ratios in the white matter that, in one study, were statistically correlated with impairments in working memory.[24,25] These findings strongly suggest that HCV infection causes brain dysfunction.

### *Cognitive impairment and hepatitis C virus treatment*

Perhaps the best evidence of a cause and effect association between HCV and neurocognition is demonstrated by the effect of viral eradication on subsequent cerebral function both using neurocognitive testing and evaluating changes in MRS metabolism.

### *Interferon treatment*

The standard of care for more than 20 years was IFN and ribavirin for HCV. IFN has direct effects on the CNS that are well recognized and include neuropsychiatric problems, such as depression, anxiety, fatigue, cognitive issues, and sleep disorders. Ribavirin is associated with anemia and insomnia with a secondary increase in fatigue. These effects occur both during treatment and, in some cases, up to 6 months after treatment and would obviously mask improvements in HCV-induced cognitive dysfunction. Some studies have demonstrated diffuse slowing on quantitative EEG and reduced performances on a cognitive screening measure early during IFN-$\alpha$ therapy, which reversed after the end of treatment.[26–28]

Studies have also shown that patients with HCV treated with IFN performed significantly worse than the untreated patients on a measure of complex attention and working memory suggesting that frontal-subcortical systems are adversely affected by IFN-$\alpha$ and that the prefrontal lobe functions of working memory may be the most vulnerable.[29–31] Interestingly, 16% of their patients with HCV continued to complain of cognitive problems after completion of IFN.

In the IFN era of treatment, sustained virologic response (SVR) was defined as no evidence of HCV RNA by a sensitive polymerase chain reaction 12 to 24 weeks after stopping all treatment. At this time point, most of the deleterious effects of IFN on cognition have resolved. Byrnes and colleagues[32] evaluated the effect of SVR prospectively in a well-controlled pilot study of 15 patients with mild fibrosis treated with pegylated IFN and ribavarin (RBV) compared with a matched control population of 7 patients with HCV who did not undergo treatment. MRS and neurocognitive testing were performed at baseline before starting, at week 12 on treatment, and at week 12 after treatment. Thirteen of the 15 treated patients completed the IFN treatment; 8 had an SVR, and 5 remained HCV RNA positive at the week 12 posttreatment time point. MRS was performed on a 3T magnet and targeted ratios of NAA, Cho, and MI compared with Cr in the left basal ganglia, left frontal cortex, and the left dorsolateral prefrontal cortex (DLPFC). The entire population had similar MRS findings at baseline, and the control untreated HCV population had no change in MRS findings over the time period showing the stability of the MRS testing. In the IFN-treated patients there was a significant decrease in both Cho/Cr and MI/Cr in the basal ganglia of patients who achieved SVR at week 12 after treatment, which was not seen in the nonresponder/relapser patients. Reductions in Cho/Cr of 24% were also seen in the DLPFC of SVR patients, but this did not reach statistical significance. No significant changes were seen in NAA/Cr at any site or time point. These changes in cerebral MRS had a clinical correlate with neurocognitive testing in patients achieving SVR who had significant improvements in total verbal learning recall, verbal memory recognition, and visuospatial memory.

In such a relatively small but well-controlled study, the findings support a substantial link between HCV and cerebral dysfunction by demonstrating a reduction in spectroscopic cerebral markers of inflammation associated with an improvement in neurocognition only seen in patients who achieved SVR.

### *Direct-acting antiviral treatment ± ribavirin*

Since 2013, most patients have been treated with direct-acting antiviral (DAA) therapy for HCV; thus, the confounding effects of IFN are removed from studying neurocognition. ION 1 was a large randomized controlled study of ledipasvir and sofosbuvir with or without RBV for genotype 1, treatment-naïve patients with HCV.[33] Alsop and colleagues[34] performed a small substudy within ION 1 whereby they examined MRS in 14 noncirrhotic subjects, 7 treated with ledipasvir/sofosbuvir (LDV/SOF) alone

and 7 with LDV/SOF + RBV. MRS was performed at baseline before treatment, at week 4 on treatment, and at week 12 after treatment using a similar protocol as described earlier for the Byrnes and colleagues'[32] study. Mental health (MH) and fatigue-related items of patient-reported outcome (PRO) questionnaires (36-Item Short Form Health Survey [SF-36], Functional Assessment of Chronic Illness Therapy–Fatigue, Chronic Liver Disease Questionnaire-HCV [CLDQ-HCV]) were assessed in all subjects at the same time as MRS was performed.

All subjects had normal alanine aminotransferase and undetectable HCV RNA at week 4 and achieved SVR. MRS demonstrated an increase in basal ganglia NAA/Cr at 4 weeks and a highly significant increase at the week 12 SVR time point, which was more profound in those subjects not receiving RBV and indicated an improvement in neuronal health. Statistical comparisons with the changes in PRO and MRS were very limited by the sample size, but some very interesting trends were seen at the week 12 SVR time point. Looking at individual subjects, an improvement in the MH component of SF-36 was observed in 9 subjects, no change in 2, and a decrease noted in 3. Of the 9 subjects for whom the MH scale of SF-36 improved, 8 subjects had a decrease in their basal ganglia Cho/Cr ratio; whereas for the 5 subjects whose MH scale of SF-36 worsened (or did not change), all of them showed an increase in their basal ganglia Cho/Cr.

Similar findings were seen in basal ganglia MI/Cr and the emotional domain (EM) of the CLDQ-HCV. Of individual subjects, 10 had their EM domain scores improved. Of those, 8 had a decrease in their MI/Cr.

Overall these findings again suggested improvements in brain metabolism particularly within the basal ganglia associated with functional improvements on PRO in MH and emotion. What is of interest is the rapidity with which these changes were seen as HCV RNA was suppressed and that they were established as soon as 12 weeks after viral eradication.

### *Direct-acting antiviral treatment: no ribavirin*

More recently, Curry and colleagues,[35] from the same institution using MRS and a full battery of neurocognitive tests, performed a double-blind placebo-controlled study on 40 noncirrhotic patients with HCV, genotype 1. Twenty-six were randomized to 12 weeks LDV/SOF and 14 to placebo, with the placebo patients transferring to open-label LDV/SOF at week 4 after treatment. The primary end point was the week 4 MRS and neurocognitive tests to see what the effect of viral suppression had on cerebral function. Patients were followed with neurocognitive tests to week 24 SVR, and a subset had late week 24 MRS. Although there were some MRS changes, such as significant decline in Cho/Cr ratio in basal ganglia of LDV/SOF-treated patients, there was overall no major significant differences at week 4 in either MRS or neurocognitive testing between the active and placebo arms. The full study has not been published, but the investigators concluded that at an early (week 4 after treatment) time point there was no major benefit on neurocognition or cerebral metabolism when DAA was compared with placebo. However, by week 24 all treated patients had evidence of improved neurocognition, suggesting that the CNS manifestations of HCV are probably not related to active replication within the brain and that the improvements occur slowly over time and require at least 24 weeks after SVR.

### *Hepatitis C virus and cerebrovascular disease*

There has been a reported association between an increase in carotid arterial plaques and HCV using cross-sectional imaging studies,[36–38] and positive strand HCV RNA has been found in studies of carotid plaques.[39] HCV is associated with serum

lipoproteins and can induce oxidative stress and localized inflammation, and all of these features can result in an increased risk of carotid plaque formation.

More importantly, multiple studies have now shown the association between HCV and stroke. Liao and colleagues[40] in Taiwan followed 4094 adults with HCV compared with a matched population of 16,376 adults without HCV. Multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for potential associated factors, including HCV infection, age, sex, low-income status, urbanization, cessation of cigarette smoking, alcohol-related illness, obesity, history of chronic diseases, and medication use.

The cumulative risk of stroke for people with hepatitis C and without hepatitis C infections was 2.5% and 1.9%, respectively, with an adjusted HR of stroke of 1.27 (95% CI 1.14–1.41) for people with hepatitis C indicating that HCV is an independent risk factor for stroke. Lee and colleagues,[41] in a second large community cohort study from Taiwan of 23,665 participants, showed an increased risk of cerebrovascular mortality with a risk-adjusted HR of 2.18. Interestingly, the risk-adjusted HR increased as the HCV RNA increased in the population, suggesting a direct effect of HCV on cerebrovascular risk. Finally, in a large meta-analysis by Ambrosino and colleagues,[42] both an increase in cardiovascular risk and cerebrovascular risk was confirmed with an odds ratio of 1.48 for cerebrovascular events. These studies clearly show an independent and significant association between HCV and risk of cerebrovascular disease. Unfortunately, no data exist as to the effect of SVR on subsequent coronary or cerebrovascular risk.

## SUMMARY

The neurologic manifestations of HCV are both common and significant with both an increased morbidity and mortality. HCV-induced neurocognitive dysfunction should be considered in patients even with mild disease, and the overall improvements reported in MH and fatigue with eradication of HCV should be considered when making treatment decisions. Patients with HCV are at risk of cerebrovascular events, and studies to evaluate the effect of eradication of HCV on subsequent vascular risk should be undertaken.

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