

# Cognitive Improvement After HCV Eradication: Extending the Benefits

See Article on Page 497

A direct effect of the hepatitis C virus (HCV) on the central nervous system (CNS) was proposed over 10 years ago as a mechanism for the neurocognitive impairment reported in this infection.<sup>1</sup> A number of studies have shown impairments in working memory, attention, executive function, and processing speed in patients with noncirrhotic HCV infection.<sup>2</sup> However, despite the many patients treated in the last decade, there have been no published studies on the effect of successful antiviral treatment on neurocognitive function in large prospectively studied cohorts. Over this period,  $\alpha$ -interferon has remained the backbone of antiviral regimens and the CNS effects of this administered cytokine have been intensively studied during treatment.<sup>3</sup>

It is well established that  $\alpha$ -interferon induces depressive symptoms in patients with HCV infection, which generally peak after 12 weeks of therapy. Other neuropsychiatric effects include fatigue, irritability, anxiety, and cognitive symptoms such as memory disturbances and concentration problems.<sup>3</sup> The underlying mechanisms of  $\alpha$ -interferon-induced depression have been studied by researchers with an interest in the inflammatory hypothesis of depression and include alterations in the hypothalamic-pituitary-adrenal axis, perturbations in the metabolism of major neurotransmitters, and the activation of the enzyme indoleamine-2,3-dioxygenase (IDO), which leads to the degradation of tryptophan into neurotoxic pathways.<sup>3</sup> In parallel, predictors of  $\alpha$ -interferon-induced depression have been sought and include genetic polymorphisms in the serotonin transporter and immune genes, blood levels of certain cytokines, e.g., interleukin-6, and other

peripheral biomarkers such as docosahexaenoic acid.<sup>3</sup> However, there has been relatively little attention paid to the *interaction* between HCV-associated cognitive impairment and the on-treatment and delayed effects of  $\alpha$ -interferon-containing therapy.

Fontana et al.<sup>4</sup> studied neurocognitive function in a cohort of patients with advanced fibrosis and cirrhosis who had previously failed to respond to pegylated  $\alpha$ -interferon and ribavirin in the HALT-C study. When retreated for a prolonged period with low-dose maintenance pegylated  $\alpha$ -interferon, they found no effect of treatment on cognitive function after up to 48 months. At baseline there was significant impairment in 28% of patients but no significant positive or negative effect of interferon was seen through treatment, raising the possibility that this group had minimal hepatic encephalopathy (MHE), which was unaffected by treatment. This study was not designed to evaluate the effect of viral eradication on neurocognitive function.

In contrast, in an earlier study<sup>5</sup> before the one published in this issue by Kraus et al.,<sup>6</sup> the same investigators reported a significant negative impact of  $\alpha$ -interferon on vigilance, attention, and working memory in patients after 3-8 months of full-dose  $\alpha$ -interferon-based treatment. There was a return to baseline cognitive function 6 weeks after the end of treatment but, again, the study was not designed to evaluate the effect of successful viral eradication. In contrast to the HALT-C cohort, this cohort had milder liver disease and the adverse effect of treatment was probably related to an absence of preexisting MHE and a higher dose of  $\alpha$ -interferon.

In this issue, the same group now report significant improvement in neurocognitive function at least 12 months after the end of successful viral eradication with pegylated  $\alpha$ -interferon-2b and ribavirin.<sup>6</sup> The group performed a series of tests evaluating executive function, including working memory and vigilance before and after therapy with a standard interferon and ribavirin regimen. The article is important in that it shows that in a “real-life” cohort of patients, there was improvement in cognitive function in patients who had a sustained virological response but not in those who failed to clear the infection. This suggests that, after the established adverse effects on interferon and ribavirin have receded, at least 12 months

Abbreviations: CNS, central nervous system; HCV, hepatitis C virus; IDO, indoleamine-2,3-dioxygenase; MHE, minimal hepatic encephalopathy.

Address reprint requests to: Daniel M. Forton, Department of Gastroenterology and Hepatology, St George's University of London, London, UK. E-mail: dforton@sgul.ac.uk.

Copyright © 2013 by the American Association for the Study of Liver Diseases.

View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).

DOI 10.1002/hep.26481

Potential conflict of interest: Nothing to report.

postcompletion of therapy an improvement in cognitive function attributable to viral eradication *per se* is evident. This reinforces the notion of a biological effect of HCV infection within the CNS. Although it is possible that knowledge of the treatment outcome might have affected cognitive performance in some way, it would not be feasible in a prospective study of this nature to blind patients to their treatment outcome for 12 months after the end of treatment.

The cohort that was studied had a relatively high sustained virological response rate and presumably did not include patients with multiple negative predictors of interferon response such as African Americans, obese individuals, and a high burden of advanced fibrosis. Although some patients with cirrhosis were studied, post-hoc analyses did not show this to be important in predicting cognitive dysfunction. This is important, as it suggests that preexisting MHE in cirrhosis nonresponders was not a confounding variable.

The finding of cognitive improvement that is independent of cirrhotic morphology is important because it adds impetus to further evaluating cognitive function as an indication for and as an outcome measure of antiviral therapy at a precirrhotic stage. Disentangling the relative contributions of HCV, cirrhosis, comorbid conditions, and concomitant medications can be challenging since available tests are sensitive but not specific.<sup>7</sup> MHE uniquely affects visuo-construction skills, motor speed, and motor accuracy, while precirrhosis HCV infection affects working memory and the domains of attention, executive function, and processing speed are affected in both.<sup>8</sup> The authors applied a relatively narrow battery of only four tests (alertness, divided attention, vigilance, and working memory), which were previously shown to be sensitive to the effect of interferon but are not specific to this or the effect of HCV infection itself. In this study, there was no comparison of baseline function with normative control data and the clinical significance of the improvement was not defined. Indeed, in future studies it will be important to link neurocognitive test performance with outcomes that affect daily life such as cognitive health-related quality of life, e.g., MOS-Cog, or Sickness Impact Profile, in order to increase acceptance of the effect on cognition as a valid outcome and as an added benefit of HCV therapy.

Despite increasing interest and research, there remains uncertainty around the mechanism of HCV-associated cognitive impairment and other CNS effects. Imaging studies have suggested evidence of CNS immune activation<sup>1,9,10</sup> and alterations in neurotransmission in HCV

infection,<sup>11</sup> yet it is unclear whether this is associated with a direct effect of viral penetration into the CNS<sup>12</sup> or a result of peripheral factors acting across the blood-brain barrier. HCV genomes have been isolated by a number of groups in human microglial cells<sup>13</sup> and recent data show that human brain endothelial cells support productive but low-level infection by HCV.<sup>14</sup> The potential importance of an extrahepatic, immune-privileged site goes beyond the neurocognitive symptoms in this infection, particularly as we move into the era of interferon-free, direct-acting antiviral therapy. The expected major improvements in sustained virological responses after finite short-course combination therapies will depend on adequate drug penetration to all sites.

The era of interferon-free regimens will greatly reduce the neurocognitive burden posed by interferon and offers further opportunities to test the relationships between HCV infection and CNS symptoms. In the absence of the deleterious effect of interferon, we should expect an accelerated improvement in neurocognitive symptoms if, as suggested, they are directly attributable to HCV *per se* and the promise of high-level, permanent viral eradication becomes reality.

JASMOHAN S. BAJAJ, M.D., M.Sc.<sup>1</sup>

DANIEL M. FORTON, Ph.D., FRCP<sup>2</sup>

<sup>1</sup>*Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, and McGuire VA Medical Center, Richmond, VA*

<sup>2</sup>*Department of Gastroenterology and Hepatology, St George's University of London, London, UK*

## References

- Forton DM, Allsop JM, Main J, Foster GR, Thomas HC, Taylor-Robinson SD. Evidence for a cerebral effect of the hepatitis C virus. *Lancet* 2001;358:38-39.
- Senzolo M, Schiff S, D'Aloiso CM, Crivellin C, Cholongitas E, Burra P, et al. Neuropsychological alterations in hepatitis C infection: the role of inflammation. *World J Gastroenterol* 2011;17:3369-3374.
- Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaey G, Neri S, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *J Hepatol* 2012;57:1379-1390.
- Fontana RJ, Bielauskas LA, Back-Madruga C, Lindsay KL, Litman HJ, Lok AS, et al.; HALT-C Trial Group. Cognitive function does not worsen during long-term low-dose peginterferon therapy in patients with chronic hepatitis C. *Am J Gastroenterol* 2010;105:1551-1560.
- Kraus MR, Schäfer A, Wissmann S, Reimer P, Scheurle M. Neurocognitive changes in patients with hepatitis C receiving interferon alpha-2b and ribavirin. *Clin Pharmacol Ther* 2005;77:90-100.
- Kraus MR, Schäfer A, Teuber G, Porst H, Paul K, Wollschläger S, et al. Improvement of neurocognitive function in responders to an antiviral therapy for chronic hepatitis C. *HEPATOLOGY* 2013;58:497-504.
- Bajaj JS, Wade JB, Sanyal AJ. Spectrum of neuro-cognitive impairment in cirrhosis: implications for the assessment of hepatic encephalopathy. *HEPATOLOGY* 2009;50:2014-2021.

8. Weissenborn K, Tryc AB, Heeren M, Worthmann H, Pflugrad H, Berding G, et al. Hepatitis C virus infection and the brain. *Metab Brain Dis* 2009;24:197-210.
9. Forton DM, Hamilton G, Allsop JM, Grover VP, Wesnes K, O'Sullivan C, et al. Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *J Hepatol* 2008;49:316-322.
10. Grover VP, Pavese N, Koh SB, Wylezinska M, Saxby BK, Gerhard A, et al. Cerebral microglial activation in patients with hepatitis C: in vivo evidence of neuroinflammation. *Viral Hepat* 2012;19:89-96.
11. Weissenborn K, Ennen JC, Bokemeyer M, Ahl B, Wurster U, Tillmann H, et al. Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment. *Gut* 2006;55:1624-1630.
12. Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC. Identification of unique hepatitis C virus quasispecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants. *J Virol* 2004;78:5170-5183.
13. Wilkinson J, Radkowski M, Laskus T. Hepatitis C virus neuroinvasion: identification of infected cells. *J Virol* 2009;83:1312-1319.
14. Fletcher NF, Wilson GK, Murray J, Hu K, Lewis A, Reynolds GM, et al. Hepatitis C virus infects the endothelial cells of the blood-brain barrier. *Gastroenterology* 2012;142:634-643.