

## Hepatitis C treatment – Clearing the mind

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The issue of whether the hepatitis C virus (HCV) affects brain function continues to arouse interest, investigation, and debate. Symptoms such as fatigue, poor memory, and concentration (“brain fog”) are commonplace and an effect of this infection on mental health related quality of life, which is independent of liver fibrosis, is well established [1]. However, despite convergent lines of evidence pointing to a biological effect of HCV within the CNS and some hypothesised mechanisms, there remains, as yet, a lack of incontrovertible evidence to definitively prove the fact. Parallels with HIV infection are commonly drawn, where AIDS related dementia is now rare with highly active anti-retroviral therapy (HAART) but milder neurocognitive impairments can persist despite immune reconstitution and viral suppression [2]. A degenerative brain process is not seen in HCV monoinfection and there remains doubt in the hepatology community as to whether HCV is a virus that can trigger neurological dysfunction. Furthermore, there does not appear to be a clinical consensus as to whether the relatively mild neurocognitive symptoms in HCV infection represent a significant or important element of the disease.

The possibility of a cerebral effect of HCV was raised ten years ago with the publication of proton magnetic resonance spectroscopy (MRS) and neuropsychological data, which showed evidence of altered cerebral metabolism and cognitive impairment in patients without advanced liver disease [3–5]. A number of further imaging studies, using MRS [6,7], positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [8] in patients without cirrhosis have demonstrated metabolic and neurochemical brain abnormalities, which differ to those described in hepatic encephalopathy. Rather, the findings suggest an inflammatory state within the brain with altered serotonergic and dopaminergic neurotransmission. In particular, elevated basal ganglia and white matter choline (Cho) and myo-inositol (ml), measured with proton MRS and often reported relative to creatine (Cr), are consistent with glial cell activation and proliferation and parallel changes observed in cerebral HIV infection [9,10]. Reduced N-acetylaspartate (NAA) has also been reported in HIV and HCV monoinfections [6,7].

A greater number of reports have documented mild but measurable cognitive deficits in patients with HCV infection, which are not readily accounted for by the severity of liver disease, associated recreational drug use or other potential confounding factors [11]. Although the studies have varied with respect to the

degree to which confounders were excluded or controlled for and in terms of their cognitive assessment methodology, there is a reported pattern of deficits in attention, working memory and learning ability with increased reaction times and relatively preserved accuracy. The prevalence of depression and anxiety was high in these reports but there do not appear to be clear associations between affective symptoms and cognitive function. However, fatigue, perhaps the commonest symptom in HCV infection, was reported to be associated with worse cognitive performance [6].

Despite the increasing body of descriptive literature, there are very few longitudinal reports of the effect of treatment and, in particular, of the effect of successful viral clearance on brain metabolism [12]. It is in this context that the small pilot study from Byrnes and colleagues, published in the current issue, is welcome [13]. Large treatment studies have demonstrated an improvement in HRQL and fatigue after a sustained virological response (SVR) to pegylated interferon and ribavirin but these studies have not generally blinded their subjects to treatment outcome and the knowledge of a “cure” is highly likely to skew results [14]. If the hypothesis to be tested were that a cerebral abnormality is due to HCV itself, objective demonstration of an improvement of that abnormality after SVR would be highly supportive of the hypothesis. Byrnes and colleagues report their findings in a small patient cohort which was studied with proton MRS and cognitive assessment before, during and after standard antiviral treatment with pegylated interferon and ribavirin. A second group of untreated patients was also studied at two time points. Overall, there were no significant changes in cerebral MRS during and after antiviral treatment. However, a sub-group analysis of viral responders and non-responders showed significant metabolic changes over time in the responder group only, consistent with normalisation of the metabolites, previously reported as elevated in HCV infection [9,10]. Significant reductions were observed in basal ganglia Cho/Cr and ml/Cr ratios in SVRs (n = 8) but not in non-responders or relapsers (n = 6). The authors interpret this as an improvement in cerebral immune activation in those who cleared the virus. Patients in the treated and untreated groups tended to show an improvement in cognitive function over time, which was ascribed to a practice effect on the cognitive battery. However, when responders and non-responders were compared again, SVRs demonstrated significant improvements in verbal learning, memory, and visuospatial memory, which were not seen in the non-responders.

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## Editorial

This study is important because it is the first to demonstrate that successful clearance of HCV infection can result in changes in cerebral metabolism that may underlie improvements in neurocognitive performance. The obvious weakness in this paper, which limits the conclusions that can be drawn at this time, is the small sample size. The significant findings are only seen in a sub-group analysis, with very small groups. It is possible that a treatment effect was not seen in the non-responders because of a type II error. Furthermore, the absence of a healthy control group prevents conclusions about the importance of the observed changes. In a study published this year, Pattullo and colleagues also used MRS to assess the effect of SVR on brain metabolism [12]. In a larger study of 40 patients (31 SVRs and 9 non-responders) significant increases in globus pallidus Cho/Cr and NAA/Cr were seen in SVRs after treatment compared to baseline. These changes were not associated with cognitive measures, which did not improve with viral eradication. The opposite effect of viral eradication on Cho/Cr in the report from Byrne and colleagues is not readily explained but may be related to different patient characteristics, voxel position and acquisition parameters. Pattullo does however report reductions in globus pallidus NAA/Cr at baseline compared to controls, which increased significantly in the SVRs. Despite this, the authors concluded that when all other causes for cerebral dysfunction are excluded, viral clearance does not contribute to significant changes in brain function or biochemistry.

There are a number of strands of evidence, in addition to clinical data, that support a biological effect of HCV on the brain. Positive and negative strand HCV genetic sequences have been amplified from RNA extracted from human post-mortem brain samples and quasispecies analyses suggest replication within the CNS, albeit at a low level [15,16]. Immunohistochemical staining for HCV non-structural protein 3 (NS3) in brain tissue suggests that astrocytes and microglia might be the host cell for HCV infection [17]. Gene expression analysis in laser dissected microglia, which stained with antibodies against HCV NS3, revealed up-regulation of proinflammatory genes such as *TNF alpha* and *IL-1b* that was not seen in NS3-ve microglia or in cells from HCV-ve individuals [18]. There are emerging *in vitro* data to support neuroimmune activation by HCV [19] and a recent report demonstrated that a human neuroepithelioma cell line expressed HCV entry receptors and allowed productive infection by the JFH-1 HCV strain, being the first non-hepatocyte line to do so [20].

These studies lead to the hypothesis that certain HCV variants or strains may gain entry to the CNS in susceptible individuals, to replicate at low but sufficient levels to cause immune activation of resident microglia, triggering established pathways that result in neuronal dysfunction [21]. In this hypothesis, successful viral eradication might reverse or attenuate the process, as suggested by the preliminary data from Byrnes and colleagues. If this is the case, it will be of interest to discover whether the evolving interferon-free regimes of direct acting anti-virals have the same effect or whether neurocognitive impairments could persist as in the case of HAART for HIV infection. Alternatively, one might consider that eradication of HCV from the liver results in normalisation of a chronic low-level inflammatory state, with concomitant improvements in brain function and metabolism secondary to a reduction of abnormal signalling, possibly by cytokines, from the periphery across the blood brain barrier.

The pilot study from Byrnes and colleagues is small but it serves to re-energise the debate as to whether there is a virological effect of HCV on brain function. A better knowledge of this is important

for our understanding of the natural history of this infection and the symptoms it causes and for our ability to design appropriate therapeutic regimes. Further large studies are now indicated to determine whether successful antiviral treatment is definitively associated with improvements in brain biochemistry and function.

### Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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