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Expert opinion on managing chronic HCV in patients with neuropsychiatric manifestations

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Abstract

Neurological manifestations of hepatitis C virus infection appear to be under-recognised in clinical practice despite the majority of HCV-infected patients experiencing symptoms such as fatigue, depression, and cognitive dysfunction. There is also growing evidence for a link between HCV infection and an increased risk of Parkinson's disease. The mechanism underpinning the association between HCV and these neuropsychiatric syndromes still requires further investigation. Here we review the pre-clinical and clinical evidence for a link between HCV and effects on the CNS leading to neuropsychiatric syndromes. Lastly, we describe how improvements in neuropsychiatric manifestations of HCV following treatment have been observed, which is subsequently reflected in an overall improvement in health-related quality of life.

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Introduction

It is estimated that approximately 71 million people worldwide have hepatitis C virus (HCV) viremia and are at risk of developing the long-term complications of chronic HCV infection, including cirrhosis, decompensated liver disease, and hepatocellular carcinoma [1]. Not all patients with chronic HCV infection develop the hepatic complications of the disease; however, 65 to 75% of patients experience neuropsychiatric symptoms [2-4]. Despite these findings, HCV is under-recognised in general practice as a cause of fatigue, and neuropsychiatric symptoms are generally under-recognised as a justification for antiviral treatment. Nevertheless, clinical guidelines recommend treatment of patients with clinically significant extrahepatic manifestations of the disease, such as disabling fatigue [5].

Neuropsychiatric phenomena associated with chronic HCV infection include fatigue, depression, anxiety and sleep disturbances, which are reflected in impaired health-related quality of life (HRQOL) and decreased work productivity, as well as neurocognitive dysfunction, which may be less obvious at the time of diagnosis [6-8]. More recently chronic HCV infection has been associated with an increased risk of developing Parkinson's disease [9,10]. The objective of this paper is to provide an overview of evidence that: HCV is present in the CNS of patients with chronic HCV infection; that chronic HCV infection is associated with neuropsychiatric symptoms; and that improvement of neuropsychiatric symptoms may be achieved by eradication of the HCV with antiviral treatment.

Evidence for HCV infection in the CNS

HCV RNA has been detected in brain samples collected post-mortem from patients with chronic HCV infection, although on this basis it is not possible to conclude whether this phenomenon was the result of productive infection or post-mortem breakdown of the blood–brain barrier [11-14]. Low-level replication of HCV RNA is, however, suggested by the detection of the negative strand of HCV RNA and by the presence of distinct quasispecies in brain samples [12-14]. HCV RNA titers in brain tissue are 1000-fold lower than in liver tissue samples from the same patients suggesting that the brain is a less effective site of viral replication [14].

HCV RNA has also been recovered from the cerebrospinal fluid (CSF) of patients with HCV infection and cognitive impairment. Of note, evidence of viral evolution was evident in envelope sequences of virus recovered from the CSF from two of four HCV-infected patients with cognitive impairment, but not from the two patients without cognitive impairment [15].

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Microglia and astrocytes are targets for HCV infection in the CNS [16,17]. In a post-mortem study of brain tissue from HCV-positive patients, amplification of RNA from cells that stained positive for HCV non-structural protein 3 (NS3) and the microglial marker CD-68 resulted in expression of microglial markers and pro-inflammatory genes for cytokines such as TNF- α and IL-12 [17]. In contrast, NS3-negative cells from HCV-positive patients and from HCV-negative controls did not express pro-inflammatory genes [17]. These data suggest that HCV infection results in immune activation in microglial cells. However, it must be noted that neither microglial cells nor astrocytes express the receptors required for entry of HCV (Fletcher et al., 2012, *Gastroenterology*, 142(3):634-643), which indicates that the presence of HCV-related material in these cells may represent cell–cell transmission from endothelial cells or alternatively, transmission from peripheral immune cells trafficking into the brain.

Sustained activation of extracellular signal-related kinase (ERK)/signal transducer and activator of transcription 3 (STAT3) system via toll-like receptor 2 (TLR2) is thought to play a role in neurodegeneration. The presence of HCV core protein resulted in sustained activation of ERK signaling in a neuronal cell line [18]. Moreover, ERK activation, dendritic shortening, reduced neuronal density, astrogliosis and cytoskeletal disruption were observed after injection of HCV core protein into murine hippocampi [18].

It was proposed that HCV might enter the CNS through infected monocytes that cross the blood–brain barrier. However, in the first demonstration of HCV replication in intracranial cells, cultured brain microvascular endothelial cells (BMEC) were infected with HCV and subsequently released particles that, in turn, infected Huh-7 hepatoma cells [19]. Once infected with HCV, BMEC undergo apoptosis, which is interpreted to reflect potential disruption of the blood–brain barrier. Disruption of the blood–brain barrier in this manner would allow peripherally-derived virus, immune cells and cytokines to gain access to, and initiate, immune activation in the CNS.

Although there is evidence that HCV can cross the blood–brain barrier, there are few data on the ability of direct acting antivirals (DAAs) to do likewise. As a result little can be said about the pharmacokinetics of DAAs in cerebrospinal fluid. However, sofosbuvir is reported to be a substrate of p-glycoprotein and, as such, may not readily penetrate the CNS [McQuaid; Soriano Expert Opin Drug Metab Toxicol 2017].

Fatigue

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Persistent, debilitating fatigue is a common complaint in patients with chronic HCV infection who are seen by health care practitioners. The prevalence of fatigue in untreated cohorts ranges from 20% to 92% depending on the cohort and the method used to assess this symptom [20-25]. In addition, one study observed persistent fatigue despite clearance of the virus after treatment in 85% of patients analyzed (N=159) [26]. The severity of fatigue is not correlated with the severity of hepatitis as indicated by serum ALT levels [27-29]. In one study, the severity of fatigue, depression, anxiety and pain was associated with significant increases in a panel of serum inflammatory factors suggesting that peripheral immune activation is related to these symptoms in patients with chronic HCV infection [30]. However, fatigue is a multidimensional symptom influenced by physical, psychological and social factors, so it is unlikely that the severity of fatigue and other neuropsychiatric symptoms in patients with chronic HCV infection can be attributed exclusively to immune activation. There is currently no clinical consensus regarding the measurement and definition of significant fatigue in HCV infection, although the Fatigue Impact Scale with a cut-off of 45 has been used in research studies [26].

Depression

Depression is a common comorbidity in patients with chronic HCV infection who are currently not receiving treatment [29,31-35]. Given that HCV can enter and replicate within the CNS, it is plausible that HCV-associated depression is a biological phenomenon. Depression is also a side-effect associated with interferon-based treatments, and there is evidence that immune cell activation and production of pro-inflammatory cytokines may play a pivotal role in the aetiology of interferon-associated depression [36]. However, the association between depression and HCV infection is multifactorial. In North America, the prevalence of HCV infection is considerably higher in patients with severe psychiatric morbidity than in the general population (17.4% versus 1%, respectively) [37]; thus, patients with chronic HCV infection may be more likely to have a pre-existing psychiatric diagnosis. Moreover, the predominant mode of HCV transmission in Western countries is injection drug use, and individuals with a history of injecting drugs have a higher prevalence of depression than non-infected subjects [38]. Finally, anxiety and reactive depression may result in receipt of a diagnosis of HCV infection or from HCV-associated fatigue and cognitive impairment [21]. Nevertheless, increased anxiety and depression scores, although not commensurate with clinical depression [39], have also been observed in HCV patients without any prior psychiatric diagnosis or history of drug abuse, the majority having been

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infected via transfusion or treatment with blood products [6]. Thus, mood alterations may well be ascribed to HCV infection. Furthermore, when considering the data provided by self-assessment questionnaires, it must be emphasized that abnormal scores in these questionnaires are not tantamount to the diagnosis of depression and can be influenced by physical symptoms such as fatigue. Compared to an expert clinical assessment, false positive as well as false negative results may be expected [39].

Cognitive dysfunction

Neurocognitive impairment has been reported in patients with mild liver disease due to chronic HCV infection [33,40] and has been reported to be more marked in patients with more advanced liver fibrosis; however, impairments in attention and concentration were still evident in up to 50% of noncirrhotic patients [23,41], although other confounding factors are likely to contribute. Some authors have found pronounced executive deficits in fatigued patients with chronic HCV infection [40], whereas others have reported no association between neurocognitive dysfunction as measured by objective tests and subjective complaints of fatigue [41]. It should be noted that several studies have reported no or minimal impairment in cognitive function in patients with HCV infection [42-45].

If present, the pattern of cognitive impairment in patients with chronic HCV infection is similar to that associated with HIV infection, suggesting that they share a common pathogenesis. Indeed, the degree of cognitive impairment is greater in patients with HCV/HIV-co-infection than in patients with HIV mono-infection, suggesting that HCV/HIV-co-infection may potentiate cognitive impairment [46].

Further evidence of this phenomenon is provided by the results of a study from the Manhattan HIV Brain Bank cohort [47], and a study that used a voice-activated Stroop task to evaluate reaction time [48]. In the former study, patients with HCV/HIV-co-infection had significant cognitive motor impairment when compared with patients with HIV mono-infection [47]. Consistent with this finding, patients with HCV/HIV-co-infection enrolled in the latter study had significantly slower reaction times than patients with either HCV or HIV mono-infection, which in turn were significantly slower than healthy controls [48]. It must be noted, however, that the findings of Martin et al [48] may be confounded by the duration of infection, long-term effects of intravenous drug abuse and severity of liver disease.

Neuroimaging studies

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Although many studies have documented neurocognitive impairment in patients with HCV infection and HCV/HIV-co-infection, it is difficult to determine the extent to which these impairments are attributable to the virus or to the effects of progressive organ dysfunction and comorbidities. For this reason, investigators have turned to neuroimaging techniques such as magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single photon emission computed tomography (SPECT) to more closely evaluate biological phenomena associated with neuropsychological impairment in patients with HCV infection.

MRS is used to evaluate metabolite concentrations in specific brain locations that are associated with neuropsychological impairment. For example, in patients with HIV, increased concentrations of myoinositol and choline in frontal white matter are associated with cognitive impairment [49]. Both myoinositol, which is primarily located in astrocytes and microglial cells, and choline, which is a marker of cell membrane synthesis and turnover, are elevated in inflammatory processes [50]. N-acetyl-aspartate (NAA) is a specific neuronal marker used in MRS studies. Decreased NAA concentrations indicate compromised neuronal integrity.

MRS has been used to study the metabolic characteristics of cerebral tissue in patients with chronic HCV infection. The first such study revealed metabolic differences (elevated choline/creatine ratio) in the white matter and basal ganglia of HCV-infected patients with minimal fibrosis when compared with those in hepatitis B virus (HBV)-infected patients and in healthy controls [51]. This pattern is distinct from that observed in patients with hepatic encephalopathy (decreased choline/creatine ratio) [52]. Exclusion of patients with cirrhosis from such studies is important because it minimizes the possibility for confounding because of minimal hepatic encephalopathy. A subsequent study of 30 non-cirrhotic patients with chronic HCV infection and mild or moderate fatigue showed evidence of cognitive impairment, primarily related to attention and executive function, and significant decreases in the NAA/creatine ratio in the cerebral cortex by MRS [40]. In contrast, motor performance and visuospatial function, which are typically affected in minimal hepatic encephalopathy, remained intact, suggesting an independent effect of HCV infection. The association between brain metabolites and cognitive scores was not especially strong in this cohort. In another study, elevated white matter and basal ganglia choline/creatine ratios were reported in patients with mild liver disease compared to control patients who either recovered spontaneously from HCV infection or who achieved a sustained virological response (SVR) after antiviral therapy [33]. These findings were independent of a history of intravenous

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drug use, depression, or fatigue. Compared to patients with HCV clearance, viraemic patients showed impairment in concentration and working memory; however, the impact of antiviral therapy on cognitive function remains unknown and has not been adequately investigated.

Elevated choline and reduced NAA levels were detected by MRS in the white matter of the brains of 37 patients with HCV infection, minimal fibrosis and minimal comorbidities [43]. This cohort was selected to eliminate factors that influence cognition, and, not surprisingly, the degree of neurocognitive impairment was minimal. HCV-positive patients had higher levels of fatigue and depression than healthy controls in this study, although there was no correlation between these parameters and cognitive ability.

Elevated myoinositol/creatine ratios in white matter have been reported in MRS studies of patients with chronic HCV infection. A significant association between the myoinositol/creatine ratio and deficits in working memory were observed in patients with mild liver disease in one study [53], and between the myoinositol/creatine ratio and both fatigue and cognitive performance in another [54]. In contrast, a negative correlation between myoinositol levels and fatigue was reported in a study in 53 patients with chronic HCV infection, minimal fibrosis, elevated choline concentrations in white matter, and elevated choline, NAA and N-acetyl-aspartyl glutamate concentrations in basal ganglia [55].

Reduced NAA/creatine levels in frontal and parietal white matter have also been reported in a study of 15 HCV-positive patients who also had lower relative cerebral blood flow than a cohort of healthy controls [56].

Collectively, the results of MRS studies suggest that cerebral metabolite abnormalities are associated with chronic HCV infection and may be evidence of an underlying neuro-inflammatory process, although the pattern of abnormalities is inconsistent. The inconsistencies in metabolite abnormalities likely reflect differences in MR parameters, data analysis and neuropsychological assessments.

Perfusion weighted imaging techniques have been used to evaluate cerebral blood flow, and diffusion tensor imaging has been used to evaluate microarchitecture in patients with chronic HCV infection. Studies have revealed decreased cerebral blood flow in the cortex and increased blood flow in the basal ganglia that are correlated with perturbations in metabolite ratios [56,57]. The results of diffusion tensor imaging studies have produced conflicting results. Increased diffusivity in the fronto-occipital cortex was associated with higher fatigue scores and increased myoinositol levels in white matter in

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patients with chronic HCV infection when compared with controls in one study [54]. Bladowska et al [56], however, observed a decrease in diffusivity in several white matter tracts in their study. One other study also found significantly decreased fractional anisotropy (an index of microstructural integrity) in asymptomatic HCV positive patients on sensory, inferior longitudinal fasciculus and STR fibre bundles compared with uninfected healthy controls [58].

Evidence of a neuro-inflammatory process is suggested by the results of PET studies that have used a ligand (PK11195) that binds to the benzodiazepine receptor expressed in activated microglia. Increased PK11195 binding in the caudate nucleus was correlated with HCV RNA levels in patients with chronic HCV infection and mild fibrosis in one study [59], and PK11195 binding in the caudate, thalamus and putamen was significantly associated with the absence of attention deficits in 22 patients with chronic hepatitis C in another study [60]. There was no difference between HCV RNA-positive and HCV RNA-negative patients in the latter study, which may indicate that mere exposure to HCV is sufficient to provoke lasting changes in the CNS.

Further evidence of the effects of HCV infection on the CNS comes from a study that used SPECT to evaluate striatal dopamine and midbrain serotonin transporter availability in noncirrhotic patients with chronic HCV infection [61]. Significant cognitive deficits were associated with reductions in availability of dopamine and serotonin transporters, and reduced glucose metabolism in the limbic association cortex, and in the frontal, parietal, and superior temporal cortices. Consistent with the study by Pflugrad et al. [60] that used PET, there were no differences between HCV RNA-positive and HCV RNA-negative patients, which suggests that HCV-associated CNS abnormalities may persist after elimination of the virus from the blood.

Few studies have examined the impact of antiviral treatment and viral eradication on neurocognitive function in patients with chronic HCV infection. Viral eradication with interferon-based therapy was associated with significant improvements in attention, vigilance, and working memory, whereas these parameters remained unchanged in patients who did not achieve an SVR [62]. In this study, cognitive outcomes were determined one year after completion of therapy to control for the well-known adverse effects of interferon-based therapy on brain function. It must be emphasized that the improvement related to the whole group's results and thus does not exclude the possibility of persisting deficits in individual patients. In another study, about half of the patients with fatigue before treatment still complained about fatigue after sustained response to interferon-based antiviral therapy [63].

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The impact of viral eradication on brain metabolism has been evaluated with MRS in a pilot study in 15 non-cirrhotic patients with chronic HCV infection [64]. Significant reductions in choline/creatine in basal ganglia were observed in patients who achieved an SVR ($n = 8$) but not in virologic relapsers or non-responders ($n = 6$). The authors also reported significant improvements in verbal learning, memory, and visuospatial memory in patients with viral clearance, although these data are not convincing. These results suggest that viral eradication may be associated with restoration of brain metabolism; however, the strength of these conclusions is limited by the small number of patients evaluated and the conclusions have been questioned [65], emphasizing the need for sufficiently powered prospective studies.

Parkinson's disease

Several epidemiological studies have reported an association between HCV infection and Parkinson's disease [66-68]. Two large studies conducted in Taiwan have established an association between HCV infection, but not HBV infection, and subsequent development of Parkinson's disease [66,67]. The largest of these studies, reviewed the medical records of 49,967 patients with viral hepatitis and 199,868 persons without viral hepatitis [67]. The crude hazard ratio (HR) for developing Parkinson's disease was 2.50 (95% confidence interval 2.07–3.02), and, after adjustment for age, sex and comorbidities, the HR was 1.29 (95%CI 1.06–1.56). By contrast, there was no association between autoimmune hepatitis, chronic active hepatitis or HIV infection and subsequent development of Parkinson's disease. More recently, a retrospective analysis of the English National Hospital Episode Statistics and mortality data identified significant associations between HCV infection (HR 1.51, 95%CI 1.18–1.9) and HBV infection (HR 1.76, 95%CI 1.28–2.37) and the development of Parkinson's disease [68]. In 2017, an analysis of a US administrative claims database was conducted to characterize the risk of PD in HCV-infected patients. The analysis consisted of a large number of interferon-era patients (treated $n = 13,655$ and untreated $n = 112,603$) and DAA-era patients (treated $n = 25,656$ and untreated $n = 140,101$). It was demonstrated that HCV infection was associated with an increased risk of Parkinson's disease (age and sex adjusted IRR = 1.621; 95%CI 1.45–1.82). In addition, treatment with DAAs was associated with a non-significant reduction in the risk of Parkinson's disease after adjustment for age, sex and baseline cofounders (IRR = 0.60; 95%CI 0.33–1.06). By contrast, no association of reduced risk was found with interferon-based treatment [9]. Lastly, a 2017 systematic review and meta-analysis of 468 studies and 323,974 participants also identified an increased risk of Parkinson's disease

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in HCV-infected patients (OR = 1.35 (95%CI 1.19–1.52) [10]. The mechanism by which HCV infection might induce Parkinson's disease in humans remains to be elucidated, although HCV has been shown to be associated with dopaminergic neuron death in a rat midbrain neuron-glia co-culture system [66].

Health-Related Quality of Life

Numerous studies have evaluated health-related quality of life (HRQOL) in patients with chronic HCV infection [41,69-77]. In general, patients with chronic HCV infection have significantly impaired HRQOL when compared with the general population, and impairment is evident across the full range of disease severity including patients with minimal fibrosis and persistently normal alanine aminotransferase levels, non-cirrhotic patients with evidence of liver inflammation, and patients with cirrhosis [69-71,76]. Prospective studies in blood donors demonstrate that impaired HRQOL is present in HCV-positive individuals who are unaware of the diagnosis when compared with HCV-negative individuals and individuals given false-positive results [78,79]. A large study by Bonkovsky et al [70] reported lower HRQOL on all eight domains of the Short-Form 36 instrument in patients with chronic HCV infection than in healthy controls. Importantly, the differences between patients and controls were statistically and clinically significant, and were greatest for scales that tend to reflect the physical aspects of the disease.

Numerous studies have shown that viral eradication, as indicated by achievement of SVR, is associated with significant improvement in HRQOL. When interferon-based therapies are used, HRQOL deteriorates during treatment because of the poor tolerability of such regimens, and then improves after completion of treatment in those in whom SVR has been achieved [73,80-82].

All-oral DAA regimens are much better tolerated and effective than interferon-based regimens, and these differences are reflected in HRQOL. An analysis of HRQOL data in patients who received boceprevir or telaprevir plus peginterferon/ribavirin in the French CUPIC trial, and who were subsequently retreated with an all-oral DAA regimen in the French SIRIUS trial, demonstrated significantly less impairment on both physical and mental component scores during treatment with the all-oral DAA regimen [83]. The results of a placebo-controlled trial suggest that improved patient-related outcomes with all-oral DAA regimens are attributable to suppression of viral replication. The trial randomized patients with chronic HCV infection to 12 weeks of treatment with sofosbuvir/velpatasvir (n = 624) or placebo (n = 116) [84]. Statistically significant improvements from baseline were obtained in

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general health, emotional wellbeing, and fatigue within four weeks in patients randomized to active treatment, but not placebo. These improvements increased throughout treatment in recipients of active treatment and were maintained after achievement of SVR. In contrast to the general improvement obtained in recipients of sofosbuvir/velpatasvir, worry scores on the Chronic Liver Disease Questionnaire-HCV instrument was the only domain in which significant improvement was obtained in placebo recipients. Multivariate analysis confirmed that active DAA treatment predicted improvement in patient-related outcomes [84].

Significant improvement HRQOL and in general health, fatigue, emotional well-being and/or physical functioning have been reported in patients who achieve an SVR12 after sofosbuvir-based treatment, including patients with cirrhosis [Younossi J Hepatol. 2014 Aug;61:228-34; Younossi et al. Hepatology. 2014 Jun;59(6):2161-9; younossi et al. Aliment Pharmacol Ther. 2018 Jan;47(2):259-267]

Of note, the presence of depression, fatigue, anxiety, insomnia and cirrhosis predict impairment in patient-reported outcomes in patients with chronic hepatitis C [Younossi J Hepatol. 2014 Aug;61:228-34; younossi et al. Aliment Pharmacol Ther. 2018 Jan;47(2):259-267]

Other trials have also confirmed that significant improvement in HRQOL becomes apparent as early as four weeks after the beginning of treatment with all-oral DAA regimens, coincides with suppression of viral replication, continues throughout treatment, and is maintained during follow-up [85,86]. Moreover, improvements obtained in these trials exceed the threshold for a minimum clinically significant difference. Positive results have been obtained in patients across the full spectrum of disease severity, including non-cirrhotic patients and patients with compensated and decompensated cirrhosis [86]. Patients with cirrhosis have greater impairment before treatment and, importantly, the greatest improvement during and after treatment is obtained in these individuals [86]. Studies with a wide range of treatment combinations have shown that ribavirin-free regimens are associated with less on-treatment impairment of HRQOL compared with ribavirin-containing regimens [81,82,85,87,88].

Although improvements of HRQOL and neuropsychiatric symptoms with successful antiviral treatment have been widely observed, it is not yet clear to what extent SVR delivers a return to normality. The studies mentioned above compare the patients' status before and after therapy, but do not include a comparison to controls. Recently it has been shown that neuropsychiatric symptoms may last and even

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worsen after spontaneous or interferon-/ribavirin-based therapeutic eradication of the virus [26]. It has yet to be shown if this holds true also for SVR after treatment with all-oral DAA regimens.

Finally, HCV infection is prevalent in people who inject drugs. As yet, little is known as to the extent to which eradication of HCV infection with DAAs may improve neuropsychological functioning in this large and important population.

Conclusion

Studies of brain tissue collected post-mortem from patients with chronic HCV infection suggest that HCV enters and can replicate within the CNS, and a growing body of evidence from neuroimaging studies suggests that chronic HCV infection is associated with pathological metabolic changes in certain brain structures. There are little data to indicate whether antiviral therapy can reverse these pathological changes or improve subtle changes in cognitive function. The recently recognised association between Parkinson's disease and chronic HCV infection is intriguing and suggests that, if left untreated, chronic HCV infection may lead to degenerative brain disease. Further studies are required to confirm these preliminary findings. Neuropsychiatric symptoms are common in patients with chronic HCV infection and are associated with diminished HRQOL. Typical symptoms include fatigue and depression, as well as subtle defects in attention and verbal reasoning. The results of large clinical studies demonstrate that eradication of HCV infection, as indicated by achievement of SVR, is associated with improvement of fatigue, HRQOL and work productivity. In patients treated with all-oral DAA regimens, these improvements become evident as early as Week 4 of treatment, and occur in concert with suppression of HCV replication and reductions in viremia. Importantly, improvements in HRQOL have been obtained across the full spectrum of disease and include patients with mild fibrosis, compensated cirrhosis and decompensated fibrosis. It is important to remember that fatigue and other CNS symptoms may be the only manifestations of undiagnosed HCV infection. Furthermore, these symptoms merit consideration alongside other arguments for timely antiviral therapy.

Acknowledgements:

Medical Editing support was provided by Gillian Patman of Medical Expressions, funded by AbbVie.

Conflicts of Interest:

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Daniel Forton: Received consulting and lecturing fees from Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Intercept, Gilead, Janssen, Merck, and Roche.

Karin Weissenborn: Received consulting and lecturing fees from Boehringer Ingelheim, Bristol-Myers Squibb, Bayer and Norgine, and research funding from Abbvie.

Mark Bondin: Employee of AbbVie and may hold stock or options.

Patrice Cacoub: Received consulting and lecturing fees from Abbvie, Astra Zeneca, Bristol-Myers Squibb, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Roche, Servier and Vifor. Pr P. Cacoub has received grants from CNRS, INSERM, Université Pierre et Marie Curie, ANRS, and WHO.

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