Depression, fatigue and neurocognitive deficits in chronic hepatitis C

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Abbreviations

HCV, hepatitis C virus; HRQOL, health-related quality of life; PBC, primary biliary cholangitis; BBB, blood-brain barrier; IL, interleukin; HPA, hypothalamic-pituitary-adrenal; RNA, Ribonucleic acid; MRS, magnetic resonance spectroscopy; HIV, human immunodeficiency virus

Key Words

Hepatitis C, Depression, Fatigue, Cognition, Quality of Life

Abstract

Patients with chronic hepatitis C virus (HCV) infection experience a range of symptoms including depression, fatigue and neurocognitive deficits, impairing quality of life. Depression, in particular, may be reactive to increased psychosocial stress, and the physical symptoms of advanced HCV or associated comorbidities. However even patients at an early stage of HCV infection, with minimal hepatic inflammation or comorbidities, report more depressive symptoms and fatigue than the general population. Similarly, specific neurocognitive deficits occur in early-stage HCV infection and are independent of the presence of depression or encephalopathy. Therefore, intracerebral neurobiological changes associated with HCV may potentially explain these symptoms. These changes may arise from infiltration of the brain by peripherally induced cytokines, as well as direct neuropathic effects of HCV viral particles penetrating the blood-brain-barrier. These phenomena parallel those reported in human immunodeficiency virus (HIV) infection. HCV-associated intracerebral changes include upregulated inflammatory responses, altered neurotransmitter levels, hormonal dysregulation, and release of neurotoxic substances. These may subsequently lead to abnormal neuronal conduction and function in areas of the brain governing affective responses, emotional processing, motivation, attention and concentration. Although direct-acting antiviral medications lead to high rates of HCV clearance, intracerebral changes may not be subsequently reversed and symptoms of depression, fatigue and neurocognitive deficits may persist. There is an ongoing role for multidisciplinary care and pharmacotherapy to manage these symptoms in HCV patients. Furthermore, there may be opportunities for future therapies to specifically target and ameliorate HCV-associated intracerebral changes.

Introduction

Chronic hepatitis C viral infection (HCV) is a global health problem affecting 1.6% of the population [1]. Mood disorders, especially depression, and fatigue are the most challenging symptoms with which HCV-related patients have to cope [2]. While direct acting antivirals have revolutionized treatment, these symptoms may continue to be a major burden in HCV patients even after viral clearance. The impact of depression and fatigue are captured when assessing health-related quality of life (HRQOL) in HCV infection, which is reduced compared to other liver diseases [3] and to the general population [4]. In HRQOL studies using the Short Form 36 Health Survey [5], depression and fatigue are represented in the emotional, mental and vitality domains and are independent predictors of poor HRQOL [6]. This is especially the case among those in pre-cirrhotic stages of disease [7], comprising up to 80% of those infected. Decreased HRQOL is independent of hepatic inflammatory activity [8]. HCV eradication generally leads to overall significant improvements in HRQOL among patients in large clinical trials [9], even among patients with established cirrhosis [10, 11]. However symptoms of depression [12] and fatigue [13, 14] may persist, as well as neurocognitive dysfunction [15] which may arise due to common causal pathways in the central nervous system.

Depression in HCV

Prevalence of depression

Pre-existing psychiatric illness in HCV, including mood and psychotic disorders, is three to four times more prevalent than in the general population [16] and often goes undiagnosed. This may be due to decreased willingness to engage with, or access to, mental and primary health care services [17]; or to real or perceived bias against HCV patients and dismissal of their psychiatric symptoms [18]. Co-morbid depression can affect prognosis as it is associated with lower adherence to HCV therapy [19].

The prevalence of depression in HCV patients is between 20 to 50% [20, 21], as compared to approximately 10% prevalence in the general population [22]. Treatment-naïve HCV patients have a significantly greater lifetime prevalence of depression when compared with age and sex-matched patients with hepatitis B infection [23] and with controls without liver disease [24]. These groups, however, do not necessarily share the same

psychosocial stressors. In the US National Health and Nutrition Examination Survey, a cross-sectional study of 10,231 patients with liver disease from HCV, hepatitis B, alcoholic liver disease and non-alcoholic fatty liver disease, only HCV was independently associated with depression [25]. This suggests additional and unique HCV-mediated mechanisms contributing to depression. The presence and severity of depression were independent of cirrhotic status, viral load, degree of hepatic inflammation and use of interferon.

Social risk factors for depression

HCV-related depression can be partially attributed to social and occupational limitations consequent on the diagnosis, including perceived restrictions in sharing food and sexual contact [26], and in obtaining certain types of employment [27]. HCV patients also have greater life stressors and fewer social supports relative to the general population [20]. These social risk factors may predate the infection, often playing a role in viral acquisition especially through intravenous drug use (IVDU). IVDU accounts for up to 80% of HCV acquisition in Western cohorts [28] and is itself strongly associated with depression [29].

Awareness of infection and social stigma contribute to psychiatric morbidity in patients with HCV [30]. Poor acceptance and shame are present in the majority of those with chronic infection, independent of socioeconomic status or educational level [26], and this correlates with depressive symptoms [21]. Indeed in some cohorts, rates of depression among patients with cleared HCV disease are similar to those among patients with chronic infection [19]; persisting life stressors, perceived stigma and poor social supports may contribute.

Physical contributors to depression

A higher burden of physical symptoms from HCV is associated with increased depression [21], and this burden increases with the complications of cirrhosis such as ascites, sarcopenia and encephalopathy causing limitations in physical and social function. A generalized inflammatory state associated with HCV may contribute to physical conditions including irritable bowel syndrome, functional dyspepsia, fibromyalgia, and chronic pain [31, 32].

Medical co-morbidity in HCV is an important contributor to depression, reduced physical functioning and poor HRQOL. Among 4,781 HCV patients in the Chronic Hepatitis C Cohort Study, higher Charlson comorbidity scores (incorporating both stage of HCV and comorbid conditions) were correlated with greater depressive symptoms [20]. Insulin resistance, diabetes mellitus, metabolic syndrome and cardiovascular disease [33] are associated with HCV; and in addition to causing physical symptoms such as weight gain, exercise intolerance or chest pain, may necessitate challenging and burdensome lifestyle changes. Inflammatory conditions such as vasculitis, cryoglobulinemia, inflammatory arthritis, immune-complex mediated glomerulonephritis and porphyria cutanea tarda [34] all commonly co-exist with HCV, causing symptoms such as arthralgia, impaired joint mobility, peripheral motor and sensory neuropathies, and skin lesions, all of which impair physical and social function [31]. Managing these comorbidities require greater use of patients' time and resources which increases psychosocial stress. Overall, reactive depression may arise from the psychosocial and physical sequelae of HCV infection [35]. Figure 1 provides an overview of pathways through which HCV causes depression through physical and psychosocial comorbidities.

The neurobiology of depression in HCV

Neurobiological structural changes may represent additional mechanisms leading to depression in HCV patients. Depression in HCV is not entirely attributable to the burden of physical symptoms and psychosocial stressors. Prospective cross-sectional studies comparing HCV patients to those with primary biliary cholangitis (PBC) found that depressive symptoms were worse in those with HCV, while physical symptoms (such as pruritus, pain and fatigue) were significantly worse in those with PBC [36]. Similarly, patients unaware of their HCV positive status report lower mood and quality of life than uninfected controls in blinded questionnaires [7], suggesting that factors apart from shame and stigma may be involved.

The generalized inflammatory state of HCV infection may affect the brain through direct and indirect mechanisms. Peripherally-derived endotoxins [37] or cytokines such as interleukin (IL) -6, IL-10 and soluble IL-2 [38] induced by HCV infection may act on the endothelial cells of the blood brain barrier (BBB), stimulating secretion of secondary messengers such as prostaglandin E2 into the brain [39]. This stimulates the release of intracerebral cytokines such as IL-1, IL-4, IL-6, IL-12, IL-18 and tumour necrosis factor alpha from activated microglia cells [40], with subsequent effects such as inhibition of neural conduction in areas of the

brain governing affective responses and emotional processing [41]; and upregulation of the hypothalamic-pituitary-adrenal (HPA) axis [42]. Intracerebral cytokines also induce enzymes such as indoleamine 2,3-dioxygenase that metabolize tryptophan into neurotoxic metabolites such as kynurenine instead of serotonin [43]. Serotonin usually binds to serotonin-1a and serotonin 1b receptors on neurons in the limbic system, causing a subsequent reduction in release of downstream inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA). Deficiencies in intracerebral serotonin may thus lead to excessive inhibitory neurotransmitter release [44], leading to depressive symptoms through reducing neuronal conduction. HCV-induced cytokines may also cross the BBB and directly exert inflammatory effects in the brain [45]. The presence of high levels of intracerebral cytokines has been associated with neurobiological abnormalities due to downstream effects including oxidative stress [46] and anti-serotonergic autoimmunity [47]. In the general population, such abnormalities in monoamine transmission and the HPA axis correlate with depression [48]. Overstimulation of the HPA axis and excess cortisol production may lead to neuronal conduction changes in the hippocampus that impair the retention of pleasant rather than unpleasant memories, worsening depression [49]. Corticotropin-releasing hormone may itself have direct neurotoxic or neuromodulatory effects [50].

Depression is known to cluster in families and inherited genetic polymorphisms may contribute to this. Specific genetic polymorphisms may affect intracerebral inflammatory responses: for example, there is an independent association in HCV patients between depression and downregulation of genes encoding molecules such as platelet factor 4 and transforming growth factor beta-1, resulting in a shift in pro-inflammatory and anti-inflammatory cytokine production [51]. Multiple other genetic polymorphisms have been associated with interferon-associated depression, although their contribution to depression outside of interferon treatment is less clear [52].

HCV, as well as other members of the flaviviridae family including Japanese encephalitis virus and West Nile virus, can cross the BBB. Autopsy studies have isolated viable HCV ribonucleic acid (RNA) from the brain [53]. Two independently derived lines of endothelial cells in the central nervous system (hCMEC/D3 and HBMEC) have been found to express specific surface receptors (claudin-1, tetraspanin CD81, E-2 glycoprotein and scavenger receptor-BI) allowing direct HCV entry and replication [54]: this appears to be specific to the central nervous system, not on endothelial cells elsewhere in the body. Viral particles may also be introduced into the brain via infected mononuclear cells and microglia [55], establishing a new reservoir of independent

viral replication. Weakening of tight junction integrity in the BBB due to virally-induced intracerebral inflammation may facilitate HCV entry, in a positive feedback loop [56]. High levels of intracerebral apolipoprotein E, produced by infected glial cells, have also been detected in HCV patients. This molecule may be important in viral assembly and act as a vector for new cell infection, amplifying this feedback loop [54].

Activated intracerebral microglia harbouring HCV infection have been demonstrated on positron emission tomography [57], which may have inhibitory or apoptotic effects on neurons through release of molecules such as pregnalone [58]. Furthermore, it has been shown that the HCV core protein causes neurotoxicity through persistent activation of extracellular signal-regulated kinase 2 (ERK2) via innate immune toll-like receptor 2 signalling, with downstream effects on neuronal apoptosis and degeneration [59]. These perturbations of the brain's inflammatory system **and subsequent impairment of neuronal function and conduction** may contribute to depression in HCV.

The effect of HCV clearance on depression

The interferon (IFN) era of treatment was hampered by the significant effects of IFN-induced depression [60], which worsened HRQOL during treatment and at the end of treatment. HRQOL, including improved mental and emotional scores was generally demonstrated at the time of sustained virological response (SVR), defined as undetectable HCV RNA 12 weeks after finishing treatment after IFN [4]. However, case series reported IFN-induced depression persisting long after treatment cessation in some patients [61], and in some cohorts HRQOL only improved 24 weeks after ceasing treatment [62].

Newer IFN-free regimens with direct acting antivirals (DAAs) have now become the standard of care to attain SVR. Compared to IFN, patients experience an improved HRQOL while on treatment [9], no matter the stage of liver disease. Phase 3 trials of DAAs have shown no significant psychiatric side effects [63-65]. Accordingly, a recent review of 5 US trials found significantly different changes in the Beck Depression score between patients receiving IFN-free and IFN-containing DAA-based regimens: depression scores worsened during treatment in the latter group but actually improved while on treatment in the former group [66].

Similarly, a large body of work has focused on improved HRQOL after DAA treatment in clinical trials, showing improvements in the mental health and emotional domains of patient-reported questionnaires after SVR. This has been demonstrated in trials of sofosbuvir/ledipasvir [10], sofosbuvir/velpatasvir [11] and sofosbuvir/velpatasvir/voxilaprevir [67]. Early improvements in HRQOL occur within the first 4 weeks of DAA treatment, as opposed to IFN-based regimens, and were also noted even in decompensated cirrhotic patients in whom IFN treatment is contraindicated [68].

Nonetheless, depression may be an ongoing issue for patients despite SVR. An analysis of 1145 patients undergoing IFN based therapy found that at 48 weeks post treatment, HRQOL had improved as an aggregate, but that improvement in the mental health domains were minimal compared to other domains such as physical functioning and vitality [69]. Another study reported similar levels of depressive symptoms in a group of 60 HCV positive women and another group of 33 with spontaneously cleared HCV infection. This study was conducted in Ireland among women who were iatrogenically infected by contaminated anti-resus immunoglobulin in 1977, and had been diagnosed only within 5 years prior to the studies. It is plausible that lingering shock or stigma from this diagnosis, even in those with spontaneously cleared infection, may have heightened psychiatric distress in this study population [70].

Managing depression in HCV

The literature regarding management of depression in hepatitis C predominantly relates to IFN-induced symptoms, which are obviated by the use of IFN-free DAA treatment regimens. However awareness of depression is still crucial in the DAA era, as depression reduces antiviral adherence regardless of regimens [71]. Multidisciplinary involvement is crucial to improve treatment adherence in patients with depression and may include dedicated mental health professionals, specialist nurses, addiction medicine specialists and social workers providing brief interventions throughout the treatment course. A randomised controlled trial assigning patients to either multidisciplinary models or standard care demonstrated improved adherence and increased SVR rates with multidisciplinary care during both IFN-containing and IFN-free regimens [72]. Peer-support groups [73], and directly observed therapy with nurses administering medications [74] are also options to improve antiviral adherence in depressed HCV patients. Such multidisciplinary interventions are also important

in managing depressive symptoms independent of antiviral treatment [75]. Self-management programs incorporating cognitive-behavioural therapy have also been shown to improve depressive symptoms [76].

Antidepressant pharmacotherapy has been used safely to treat depression in HCV patients, with selective serotonin reuptake inhibitors (SSRIs) such as citalopram [77] and escitalopram [78] showing good results in trial settings. Smaller studies have shown benefit for other common antidepressants such as bupropion, mirtazapine and tricyclics [79]. Similarly, a very small case series has demonstrated benefit with oral supplementation of tryptophan [80], a serotonin precursor. Care must be taken to avoid drug-drug interactions between antidepressants with concomitant antiviral therapy, although this is largely the case with older DAAs such as simeprevir, boceprevir and telaprevir, rather than newer regimens [81].

Fatigue in HCV

Chronic fatigue is the most common symptom in HCV, affecting between 50% to 80% of those infected [82] with a far greater prevalence than the average population. Although HCV patients report peripheral muscle fatigability, their quality of life is more significantly impacted by central fatigue with heightened perception of effort and decreased motivation to perform physical and mental activities [83]. Such central fatigue is independent of hepatic inflammation [8], cirrhotic status [84] or other medical comorbidities. However fatigue is strongly associated with depression: among 1,615 HCV patients in a French cohort, the prevalence of depression was 4.2%, 7.4% and 13.4% among those with absent, moderate and severe fatigue respectively [85]. Indeed, subjective fatigue is a well-recognized hallmark of depression, even in the absence of HCV, due to the subsequent effects of apathy, demotivation, non-restorative sleep, disinterest and lack of energy [86].

However, central fatigue and depression may have common neurobiological causal pathways, due to decreased central levels of neurotransmitters and downregulation of their receptors [87], and these pathways may be triggered by HCV infection. Reduced levels of dopamine [88] are seen particularly in the ascending reticular activating and limbic systems among fatigued patients with HCV [89], possibly from cytokine-induced reduction in tetrahydrobiopterin, an enzyme in the dopamine synthetic pathway [90]. Dopamine is thought to have important modulatory effects in neural behavioural pathways governing reward, motivation and perceived effort in performing tasks, which thus influence the subjective sensation of fatigue [91]. Decreases in serotonin-

1 receptor binding, **aforementioned as being implicated in depression**, have also been correlated with increased fatigue [92]. Central effects of upregulated corticotropin-releasing hormone on nerve fibres regulating behaviour may also play a role [93].

Successful viral clearance often improves fatigue. SVR after IFN treatment has been associated with a significant improvement in patient-reported fatigue scores, with no significant improvement seen upon treatment failure [94]. On HRQOL scores after IFN-free DAA treatment, measures of vitality and physical function greatly improve during treatment, at end of treatment and at SVR [9]. Nonetheless, some studies have reported persistent fatigue despite SVR. One study comparing 66 HCV positive women with 20 women who had cleared HCV (either spontaneously or after SVR with IFN) reported no difference in fatigue scores between the two groups, regardless of IFN use. Both groups reported greater fatigue than healthy age-matched controls [14]. Another study of 145 patients found no difference in the prevalence of chronic fatigue (nor depressive symptoms) between non-cirrhotics with previous SVR due to interferon therapy and those with active HCV infection, which was up to 85% in both groups [12]. However selection bias may have been present as patients were recruited from HCV support groups and outpatient clinics: patients who did experience improved mental health post-SVR may have ceased attending these clinics and may have been unable to be recruited.

Managing fatigue in HCV

Though literature exists regarding fatigue management for liver disorders in general, specific literature in the HCV setting is scarce. Self-management and cognitive-behavioural therapy may be useful [95], as well as structured lifestyle changes to maintain physical activity but reduce exertion [96]. SSRIs have shown some limited benefit in improving fatigue in HCV [97], as a secondary outcomes of a trial evaluating depression. A small placebo-controlled randomised trial of ondansetron, a competitive serotonin-3 receptor antagonist, found an improvement in fatigue among HCV patients [106]. While the potential mechanisms are not fully understood, they may involve a blockage of serotonin-induced GABA release in areas such as the hippocampus, dorsal raphe and prefrontal cortex [98]. Modafinil, an agent that upregulates multiple intracerebral neurotransmitters including serotonin, dopamine and histamine [99], has been shown to improve fatigue in small trials of HCV/HIV co-infected patients [100] and in a cohort receiving IFN treatment [101].

Neurocognitive deficits in HCV

Up to 50% of HCV patients show deficits on neurocognitive testing, with the greatest effect on verbal recall and working memory [102]. Impaired attention and concentration, processing speed, fine motor skills [103] and executive function [30] have also been described. **HCV-induced intracerebral mechanisms leading to depression and fatigue, as previously described, may also cause in abnormal neural conduction in areas of the brain governing these tasks. A direct virally-mediated neurotoxic mechanism is suggested by the observation that** patients with detectable HCV in the brain have greater neurocognitive impairment than those with HCV confined outside the brain [104]. Changes in electrophysiological evoked potentials [105] and magnetic resonance spectroscopy (MRS) [106] occur in HCV patients, suggesting intracerebral pathology affecting neuronal metabolism and conduction, independent of hepatic viral activity. Distinct MRS changes include increased choline/creatine ratios and increased myoinositol/creatine ratios in the basal ganglia, as well as decreased N-acetyl aspartate in the white matter. These MRS changes are different to those seen in hepatic encephalopathy. The selective neurocognitive abnormalities differ from the more global blunting seen in severe depression alone; and are independent of depressive symptoms [102], HRQOL, fatigue [107], or the presence of encephalopathy [108].

Neurocognitive deficits and brain changes on MRS may improve after viral eradication. One study compared a cohort of patients having achieved SVR after IFN treatment to another cohort with active HCV, but at a mild stage of disease to exclude possible confounding effects of cirrhosis. Higher neurocognitive function in terms of working memory and concentration was found in those having cleared HCV, correlating with lower choline/creatine ratios on MRS [109]. Several studies have administered MRS and neurocognitive testing to patients before and after antiviral treatment, demonstrating that those who successfully achieved SVR had significantly reduced choline/creatine and myoinositol/creatine ratios as well as improved neurocognitive function compared to those failing to achieve SVR, or to control groups of untreated HCV patients [110, 111]. Conversely, in some patients neurocognitive problems may persist despite SVR, as was reported in another study of forty patients wherein altered MRS findings post-SVR did not lead to significant improvement on neurocognitive testing [15]. **As yet, no treatments beside antiviral therapy have been trialled to specifically ameliorate neurocognitive dysfunction in HCV; this represents an avenue for future research.**

Figure 2 provides an overview of pathways through which HCV causes depression, fatigue and neurocognitive deficits with particular attention to intracerebral neurobiological changes.

Intracerebral effects of HCV and HIV

The body of literature about the neuropathological effects of human immunodeficiency virus (HIV) infection suggests similarities to the effects of HCV. HIV-associated depressive symptoms and neurocognitive abnormalities of decreased concentration and processing speed [112], as well as changes on MRS and evoked potentials [113], are similar to those found in HCV. Like HCV, HIV has been shown to induce neuroinflammation [114], upregulate the HPA axis [115], and penetrate the BBB to infect astrocytes and microglia [116]. Patients who are co-infected with HIV and HCV have greater levels of neurocognitive impairment than those with HIV alone, suggesting an additive effect from both viruses [117]. A brain autopsy study in HIV/HCV co-infected patients demonstrated HCV infection (as detected by immunocytochemical and PCR testing) in astrocytes and macrophage-microglial cells [118], and indeed intracerebral coinfection has been found on post-mortem studies to be associated with greater cognitive impairment [104]. FKBP5 genetic polymorphisms confer an increased risk of depression and psychosis in HIV patients [119, 120]; whether such genetic polymorphisms similarly increase the risk of psychiatric disorders in HCV patients remains an area of ongoing study.

Conclusion

HCV has systemic effects outside the liver, including intracerebral effects contributing to depression, fatigue and neurocognitive deficits. Both autopsy and *in vitro* studies have revealed HCV-associated neurotoxicity, from both peripherally-derived cytokines and direct viral penetration through the BBB. These symptoms may resolve with successful systemic viral eradication, especially with new antiviral treatments. However in some patients they persist, suggesting that HCV treatments may not be totally effective in eradicating the virus within the brain or reversing established abnormalities therein. Though many potential mechanisms have been explored, the overall neurobiology of intracerebral HCV remains incompletely understood. **This remains a focus of future research in addition to the optimal management of associated symptoms, the capability of new HCV**

treatments to penetrate the BBB, and the development of future treatments that may ameliorate or reverse HCV-associated intracerebral changes.

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Figure Legend

Figure 1: overview of HCV mechanisms causing depression through psychosocial and physical comorbidities.

HCV: hepatitis C virus. IVDU: intravenous drug use. PCT: porphyria cutanea tarda.

Figure 2: overview of HCV mechanisms causing depression, fatigue and neurocognitive deficits through intracerebral neurobiological changes. CRH: corticotropin-releasing hormone. ERK2: extracellular signal-regulated kinase 2. GABA: gamma-aminobutyric acid. HCV: hepatitis C virus. HPA: hypothalamic-pituitary-adrenal. IL: interleukin. MRS: magnetic resonance spectroscopy. TLR: toll-like receptor.

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